FIFTH EDITION

Gabbard's TREATMENTS of PSYCHIATRIC DISORDERS

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Glen O. Gabbard, M.D.

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Introduction

The first edition of *Treatments of Psychiatric Disorders* appeared in 1989 as a report of a task force on treatment of the American Psychiatric Association. Encompassing four volumes, it was encyclopedic in scope and rapidly became the leading reference on treatment in American psychiatry. This task force had gathered together panels of experts who exhaustively reviewed the treatment literature in pursuit of consensus regarding the most useful treatments for the major psychiatric disorders. Dr. Byram Karasu edited that first edition but declined to continue as editor-in-chief for the second edition. I was then invited to take his place for that version of the text. In conjunction with American Psychiatric Publishing (APP) Editor-in-Chief Carol Nadelson, we decided to reduce the book by half. Hence two volumes were published in 1995 as the second edition. The third edition came out in 2001, also in two volumes. When it came time for the fourth edition, I conferred extensively with Robert E. Hales, M.D., Editor-in-Chief of APP, and John McDuffie, Editorial Director. With the aim of making the text more user-friendly, we made a decision to reduce the size to one volume instead of two. This volume also appeared in a digital version on PsychiatryOnline, APP's online portal.

This fifth edition was postponed until the DSM-5 project was nearly completed so that the treatments catalogued and discussed in this volume would be geared to the new diagnostic nomenclature. However, to reduce the length (and weight) of this edition, we instructed the expert authors to focus almost exclusively on treatment rather than diagnostic considerations. We also asked them to delete portions of the chapters from previous editions that were no longer relevant so that the latest treatments would constitute the main focus of each chapter. As has been our tradition, we emphasize treatments that have been proven to be efficacious through research using randomized, controlled trials. Knowing that such trials are not always generalizable to naturalistic settings, we also encouraged our authors to include data from uncontrolled studies and accumulated clinical wisdom when there was little outcome research. Because of the recent shift to DSM-5 criteria, much of the research summarized in this volume is based on studies using the DSM-IV criteria but is largely applicable to treatment considerations regarding the diagnostic entities in DSM-5.

To assist us in identifying experts on treatments of the various DSM-5 disorders, we assembled an impressive group of section editors who selected the authors and consulted with them on their work throughout the writing process. The sections were also relabeled and reorganized according to the DSM-5 classification. As we have continued to be conscious of the size of the text, and the relationship of size to cost, we have consolidated the material by assigning more than one portion of the DSM-5 to one section of the text in many cases. Moreover, we have restricted the content to

the major psychiatric conditions seen in clinical practice while leaving out some conditions that are more uncommon or have limited outcome research related to the disorder. For the opening section on neurodevelopmental disorders and elimination disorders, Robert Findling, M.D., Molly McVoy, M.D., and Ginger Nicol, M.D., served as section editors. The portion of the book devoted to schizophrenia spectrum and other psychotic disorders was coedited by Carol Tamminga, M.D., and Charles Schulz, M.D. The section combining bipolar and related disorders and depressive disorders was coedited by Joseph Goldberg, M.D., and Anthony Rothschild, M.D. Anxiety disorders were placed together with obsessive-compulsive and related disorders, and this section was co-edited by Franklin Schneier, M.D., and Barbara Milrod, M.D. Trauma and stressor-related disorders were added to dissociative disorders under the editorship of David Spiegel, M.D. The section on somatic symptom disorders and feeding and eating disorders was coedited by Joel Dimsdale, M.D. for the former conditions and Allan Kaplan, M.D., for the latter conditions. Sleep-wake disorders were edited by Karl Doghramji, M.D., and Anna Ivanenko, M.D., Ph.D. Sexual dysfunctions, paraphilic disorders, and gender dysphoria were coedited by Richard Balon, M.D., and Anita Clayton, M.D. The section that collected together the group of disorders known as disruptive, impulse-control, and conduct disorders was coedited by Laura Antar, M.D., and Eric Hollander, M.D. Frances Levin, M.D., Herbert Kleber, M.D., and Marc Galanter, M.D., coedited the portion of the text devoted to substance-related and addictive disorders. Neurocognitive disorders were included in a section coedited by David Arciniegas, M.D., Stuart Yudofsky, M.D., and Robert Hales, M.D. Finally, the section on personality disorders was coedited by John Gunderson, M.D., Lois Choi-Kain, M.D., and Glen O. Gabbard, M.D.

Gabbard's Treatments of Psychiatric Disorders, Fifth Edition, does not represent an official policy statement of the American Psychiatric Association or any other body regarding which treatments must be used for which disorders. It is best described as a collection of expert opinion—the accumulated wisdom based on empirical research and clinical experience that assist clinicians in constructing a treatment plan that makes sense for an individual patient. We recognize that complex comorbidity is pervasive in psychiatric patients, and treatment information from this book must be used creatively to address multiple disorders in one patient.

Finally, I wish to express my heartfelt gratitude to the team of colleagues who worked with me on this project. The section editors have been dedicated to their tasks and conscientious in their editorial work despite having extraordinarily busy administrative, clinical, educational, and investigative workloads. At APP, Bessie Jones was diligent in keeping track of numerous versions of the chapters as they were submitted and unfailingly pleasant when she had to inform authors and section editors that chapters were overdue. Robert Hales and John McDuffie provided generous support for me in the conceptualization of the project and in the translation of the vision into the completed work. Greg Kuny managed editing and production with his usual skill and care. Carrie Farnham, Rick Prather, Tammy Cordova, and Judy Castagna also made significant contributions to production. I consider myself fortunate to have had this team as my able associates throughout my work on this fifth edition.

Glen O. Gabbard, M.D.
Editor-in-Chief

PART I

Neurodevelopmental Disorders and Elimination Disorders

Robert L. Findling, M.D., M.B.A.
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The treatment of psychiatric disorders in infancy, childhood, and adolescence has undergone substantial changes since the last edition of this text. Advances in the fields of child and adolescent psychiatry, neurology, and other related pediatric subspecialties have resulted in the development of new evidence-based, diagnosis-specific psychosocial and psychopharmacological interventions, including updates related to the recent release of DSM-5. In the following chapters, our expert colleagues summarize briefly the natural history and clinical features of selected DSM-5 disorders and then focus on evidence-based treatments for conditions under discussion. The child and adolescent section of this book has been substantively revised, and new chapters on communication disorders and elimination disorders have been added since the last edition.

First, in Chapter 1, "Intellectual Disability (Intellectual Developmental Disorder)," James Harris presents a comprehensive review of diagnostic changes in DSM-5 related to intellectual disability and how these might impact the treatment of these complex, vulnerable patients. Dr. Harris considers the system-level issues providers must address when diagnosing and treating patients with intellectual disability, reviewing the importance of psychiatric comorbidity and presenting information on a broad range of psychosocial and pharmacological treatments.

In Chapter 2, "Communication Disorders," Jason Spivey, Candice Maietti, and Molly McVoy discuss the wide range of conditions that fall into the communication disorder classification, including social (pragmatic) communication disorder, a new diagnosis included in DSM-5.

Treatment strategies, including school interventions, occupational therapy strategies, and speech therapy approaches, for these disorders are reviewed. In addition, the latest research on innovative treatment approaches is presented by the authors.

In Chapter 3, "Autism Spectrum Disorder," Bryna Siegel, Lindsay Mays, and Anna Homen present behavioral and pharmacological interventions for autism and pervasive developmental disorders that are supported by empirical research. The authors describe changes related to treatment modalities from DSM-IV-TR to DSM-5 and review the most updated research and research models, with the latest information on autism spectrum disorder. A means by which the clinician may formulate which interventions are most suitable for a particular individual with an autism spectrum disorder is also presented.

In Chapter 4, "Attention-Deficit/Hyperactivity Disorder," Sharon Wigal summarizes the literature on the treatment of attention-deficit/hyperactivity disorder (ADHD). The author presents medication dosages, side effects, indications, and contraindications, including the differential use of first- through fourth-line medications for ADHD. The latest formulations of stimulant medications and research supporting their use are described in detail. In addition, psychotherapeutic interventions are discussed in relation to the treatment of ADHD.

In Chapter 5, "Specific Learning Disorder," Arlene Young and Joseph Beitchman present the latest understanding of learning disorders and their subtypes in this rapidly changing field. Emphasizing a multimodal, multidisciplinary approach to treatment, the authors address both the core deficit in each type of learning disorder and concisely review intervention strategies that enhance functioning and facilitate appropriate development in these youngsters.

In Chapter 6, "Tic Disorders," Robert King, Michael Bloch, Denis Sukhodolsky, and James Leckman review the treatment of tic disorders. They describe behavioral intervention programs for home and school, as well as indications and guidelines for psychotherapy and family therapy. In reviewing the range of psychopharmacological interventions, the authors consider special medication issues (e.g., related disorders that may be alternative expressions of the same underlying genetic etiology) and address the controversy about whether stimulants exacerbate tics.

In Chapter 7, "Elimination Disorders," Griffin Stout, Ginger Nicol, and William Reiner provide an easy-to-understand, comprehensive description of the treatment of elimination disorders. A complicated set of disorders is made readily understandable, and treatment strategies that are accessible to clinicians are laid out in a practical way.

In summary, we believe the authors of these chapters have assembled the most current and comprehensive set of evidence-based treatment approaches available in the field today for some of the most common psychiatric disorders of childhood and adolescence.

CHAPTER 1

Intellectual Disability (Intellectual Developmental Disorder)

James C. Harris, M.D.

Emotional, behavioral, and mental disorders are diagnosed in approximately one-third of all individuals diagnosed with intellectual disability (intellectual developmental disorder) (ID[IDD]) (Cooper et al. 2007a, 2007b, 2009; Emerson and Hatton 2007; Roeleveld et al. 1997). The co-occurrence of these diagnoses in persons with ID(IDD) contributes to their overall functional disability and is an additional burden for affected individuals and families already coping with the consequences of cognitive and adaptive deficits.

Psychiatric involvement for persons with ID (IDD) dates back to the nineteenth century, when psychiatrists frequently were superintendents of early institutions for people with this disability. In more modern times, personalized psychosocial, behavioral, and pharmacological therapies have been proven to be effective treatments for people with ID(IDD) and co-occurring mental disorders (Gentile and Gillig 2012; Prout and Nowak-Drabik 2003; Reiss and Aman 1998; Stavrakaki and Klein 1986), allowing individuals to be treated in the community rather than in institutions.

This chapter reviews the evidence base for psychosocial, behavioral, and psychopharmacological treatments for people with ID(IDD) and co-occurring mental disorders. Its emphasis is on the importance of *personalized* treatment. Changes in the definition of ID(IDD) in DSM-5 (American Psychiatric Association 2013) and its potential impact on diagnosis and treatment are also discussed. Throughout this chapter, the special vulnerabilities of these individuals for co-occurring mental disorders and the importance of a devel-

opmental approach to treatment and diagnosis are emphasized.

Definition of Intellectual Disability

Intellectual disability (intellectual developmental disorder) is defined in DSM-5 as a neurodevelopmental disorder characterized by deficits in both general mental abilities and adaptive functioning with onset in the developmental period (American Psychiatric Association 2013). Components of intelligence included in the DSM-5 definition of ID(IDD) include verbal comprehension, working memory, perceptual reasoning, and cognitive efficacy. DSM is no longer a multiaxial classification, as it was in previous editions. Thus, ID(IDD) is no longer coded on Axis II but instead is diagnosed along with other mental disorders on Axis I.

The DSM-5 definition of ID(IDD) (see Box 1–1) is synonymous with the proposed ICD-11 diagnosis of intellectual developmental disorders (Salvador-Carulla et al. 2011). Although the term *disability* is used in DSM-5, the diagnosis of ID(IDD) as a mental disorder is conceptualized as a health condition like other mental disorders. Less emphasis is placed on the IQ score in DSM-5, and greater emphasis is placed more broadly on assessing personal competence. In DSM-5, personal competence is understood as linked to adaptive intelligence in the conceptual, practical, and social domains. Schalock (2011) refers to this approach as "multidimensional." In DSM-5, severity specifiers (i.e., mild, moderate, severe, and profound) are used to designate the extent of adaptive dysfunction in academic, social, and practical domains and replace the subtypes included in earlier DSM classifications.

Box 1–1. DSM-5 Diagnostic Criteria for Intellectual Disability (Intellectual Developmental Disorder)

Intellectual disability (intellectual developmental disorder) is a disorder with onset during the developmental period that includes both intellectual and adaptive functioning deficits in conceptual, social, and practical domains. The following three criteria must be met:

A. Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing.
B. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.
C. Onset of intellectual and adaptive deficits during the developmental period.

Note: The diagnostic term *intellectual disability* is the equivalent term for the ICD-11 diagnosis of *intellectual developmental disorders.* Although the term *intellectual disability* is used throughout this manual, both terms are used in the title to clarify relationships with other classification systems. Moreover, a federal statute in the United States (Public Law 111-256, Rosa's Law) replaces the term *mental retardation* with *intellectual disability,* and research journals use the term *intellectual disability.* Thus, *intellectual disability* is the term in common use by medical, educational, and other professions and by the lay public and advocacy groups.

Specify current severity (see DSM-5, Table 1, pp. 34–36):

317 (F70) Mild
318.0 (F71) Moderate
318.1 (F72) Severe
318.2 (F73) Profound

Criterion A (Box 1–1) refers to deficits in general mental abilities derived from the mainstream science definition of intelligence (Gottfredson 1997). These include reasoning, problem solving, planning, abstract thinking, judgment, and academic learning and learning from experience. The inclusion of a definition of intelligence is needed to emphasize that ID(IDD), a neurodevelopmental disorder, is a cognitive clinical entity analogous to dementia (major neurocognitive disorder). These intellectual functions are included in Criterion A to focus the clinical interview on them. The interviewer is required to clinically evaluate these general mental abilities in addition to arranging for standardized psychological testing. Deficits in adaptive functioning (Criterion B) include deficits in reasoning in conceptual, social, and practical domains. These deficits result in failure to meet developmental and sociocultural standards for personal independence and social responsibility in various settings, such as home, school, work, and community. Criterion C emphasizes that ID(IDD) is a neurodevelopmental disorder of brain functioning.

Legal Implications of the DSM-5 Definition

The U.S. Supreme Court's 2002 *Atkins v. Virginia* decision stated that mental retardation was cruel and unusual punishment and a mitigating factor in capital murder cases. This decision has resulted in an increased need for mental health experts, psychiatrists, and psychologists to testify in regard to mitigating circumstances—that is, whether the individual's presentation meets diagnostic criteria for intellectual disability and whether a co-occurring mental disorder is present (Olley 2009). Changes made in DSM-5 highlight the importance of clinical judgment in making the diagnosis. This shift in emphasis is pertinent to forensic psychiatry, because the IQ test number has often been used inappropriately to define a person's overall ability in forensic cases without adequate consideration of adaptive intellectual functioning. In forensic situations, a model, like that included in DSM-5, that considers adaptive intelligence in academic, social, and practical domains may be more appropriate than previous approaches (Greenspan and Switzky 2006). Moreover, credulity and gullibility in persons with ID(IDD) are pertinent psychological constructs to consider in both community settings and forensic cases (Greenspan et al. 2001). Those affected often are unaware of the risk and in many circumstances may lack common sense (Greenspan et al. 2011). Thus, emphasis on both cognitive deficits and adaptive reasoning is needed in forensic settings.

Etiology

ID(IDD) is associated with problems in brain development during the prenatal, perinatal, or postnatal developmental periods. These include genetic disorders, prenatal infections, gestational alcohol abuse, cerebral dysgenesis, birth injury, neonatal infections, and other acquired conditions occurring postnatally during the developmental period. The wide range of causes for ID(IDD) requires the

clinician to consider the developmental course and trajectory of each etiology in diagnosis and treatment planning.

Developmental Perspective

Deficits in general mental abilities with onset during the development period limit functioning and restrict participation and performance in activities in everyday life. Thus, persons with ID(IDD) commonly require lifelong, individualized educational, psychosocial, and/or community support. Aspects of reasoning affected include the conceptual understanding needed to master academic skills, the practical reasoning needed to master skills of daily living, and the social reasoning required to understand interpersonal relationships in family life, school, and community. Gullibility is a feature of ID(IDD) and in social situations is a particular concern because of the risk for manipulation by others (Greenspan et al. 2001). The more severe the degree of ID(IDD), the greater the risk of unawareness and the need for protection and supports. Moreover, there is failure in cognitive progression with aging, resulting in cognitive developmental thresholds (e.g., mild, moderate, severe, profound) in general mental abilities (Harris 2006). Working memory (the ability to keep past experiences in mind in seeking to master a new task), cognitive efficacy (efficiency or speed in reasoning), and executive functioning (self-regulation, impulse control, and capacity to plan) will vary with a person's cognitive capacity.

Assessment

The psychiatric evaluation of persons with ID(IDD) covers the same areas that are addressed in the psychiatric evaluation of typically developing individuals, but with minor modifications. The evaluation of those with severe and profound deficits requires greater modification and more reliance on other informants. The etiology of ID(IDD) should be established when possible, because it may clarify the prognosis, provide information on the natural history of the disability in regard to potential medical and behavioral complications, and facilitate treatment. A comprehensive assessment includes a diagnosis of ID(IDD) and its level of severity; a review of present concerns and symptoms; past and present developmental, genetic, medical, social, psychiatric, and family history; individual patient and informant interviews; review of current and past cognitive testing; physical examination; diagnostic formulation; treatment plan; an informing conference to review findings; and follow-through (Aman 1991; Szymanski and King 1999). Caregivers who know the patient well are used as informants, and data from interdisciplinary team assessments are utilized in treatment planning. Disorders of interpersonal functioning, communication, emotion, and behavior, as well as mental disorders, should be considered in the assessment. The American Association on Intellectual and Developmental Disabilities provides assessment guidelines based on the disability construct (Schalock et al. 2010).

Co-Occurring Psychiatric Disorders

Psychiatric disorders are three to four times more likely to be diagnosed in people with an ID(IDD) diagnosis than in the general population, and treatment of these co-occurring disorders can pro-

foundly impact functional outcomes (Cooper et al. 2007a, 2007b, 2009; Emerson and Hatton 2007; Roeleveld et al. 1997). Systematic investigations show that the full spectrum of psychiatric disorders can be identified among individuals with ID(IDD) (Cooper et al. 2009; Harris 2006). Children and adults with mild to moderate ID(IDD) present with psychiatric symptoms and disorders similar to those found in typically developing persons. However, significant differences in types of co-occurring mental disorders are documented in persons with severe to profound ID(IDD) (Forster et al. 2011). Consideration of and evaluation for co-occurring psychiatric disorders is critical in creating an effective individualized treatment plan.

The prevalence of *attention-deficit/hyperactivity disorder* (ADHD) and ADHD-like disorders among persons with ID(IDD) is similar to that in the general population, with the prevalence estimated to be between 4% and 11% for some syndromes (Feinstein and Reiss 1996) but higher in specific neurogenetic syndromes. The differential diagnosis must consider situation-specific hyperactivity that may be elicited when demands are too great for cognitive mastery, hyperactivity associated with neurogenetic disorders (e.g., fragile X syndrome, phenylketonuria, tuberous sclerosis) (Harris 1998), neurodevelopmental disorders (e.g., fetal alcohol spectrum disorder), and side effects of certain medications (e.g., akathisia from antipsychotics).

Disruptive and conduct disorders (e.g., oppositional defiant disorder, conduct disorder) are also common in persons diagnosed with ID(IDD). In a sample comprising 10,438 children and adolescents ages 5–15 years in England, Scotland, and Wales, Emerson (2003) found that the rate for any type of conduct disorder was 25% among children and adolescents with a diagnosis of ID(IDD) compared with 4.2% among children and adolescents in the typically developing control group.

Mood and anxiety disorders are often under- or misdiagnosed in persons with ID(IDD). Those referred for a disruptive behavior disorder may have an underlying mood disorder. The prevalence of mood disorder is equal to or greater than that in the general population, but the risk may be greater in some ID(IDD) syndromes such as Down syndrome. Loss of interest in usual activities, self-reported distress, and tearfulness may be better guides to diagnosis than self-reports of sadness on formal mental status examinations (Harris 1988). The field trials for the DC-LD (Diagnostic Criteria for Psychiatric Disorders for Use in Adults With Learning Disability/Mental Retardation) found that 101 of 709 clinical cases reviewed involved a diagnosis of an affective disorder (Cooper et al. 2003). Self-injurious behavior may accompany depression in the ID(IDD) population and requires prompt diagnostic attention, as individuals with a diagnosis of ID(IDD) with co-occurring mental disorders are at risk for suicide attempts (Ludi et al. 2012). Thus, screening for suicidal thoughts is essential in the assessment process. Anxiety disorders (e.g., generalized anxiety disorder, specific phobias, panic attacks), posttraumatic stress disorder, and obsessive-compulsive disorder have been reported, with a prevalence of 25% found in one outpatient sample (Feinstein and Reiss 1996).

The prevalence of *schizophrenia spectrum and other psychotic disorders* is generally similar in people with and without ID(IDD), although reports vary. Hallucinations, delusions, and thought disorder all require a certain level of verbal competence to evaluate, and thus they are difficult to diagnosis in subjects with an IQ lower than 45. Comparisons of intel-

lectually disabled and nondisabled patients with schizophrenia show that individuals with psychosis and ID(IDD) have an earlier age at onset than typically developing persons and a less favorable premorbid history. Velocardiofacial syndrome (22q11 deletion) is an ID(IDD) syndrome linked to psychosis; the same core schizophrenia phenotype has been reported in this syndrome (Bassett et al. 2003).

Autism spectrum disorder is more common in people with ID(IDD) (Ghaziuddin 2000), particularly in those who are more severely affected, and services are required for both diagnoses. *Impulse-control disorders and stereotypic movement disorder* (with or without self-injurious behavior) are a major concern. Self-injurious behavior is of particular concern in people with severe and profound ID(IDD); this behavior requires prompt diagnostic attention and may warrant a separate diagnosis of stereotypic movement disorder. Individuals with severe or profound ID(IDD) are more likely to demonstrate self-injury, aggression, and disruptive behaviors.

Treatment

Treatment of psychiatric disorders in children and adults with ID(IDD) must consider the complex interplay of neurobiological and psychosocial factors. Improved environmental provisions; educational (and cognitive) interventions and skill development; individual, family, and group psychotherapy; family interventions; behavioral interventions; and pharmacotherapy—all should be considered.

Environmental Provisions

Appropriate living conditions, vocational opportunities, and structured leisure time activities are essential environmental provisions for persons with ID(IDD). It is especially important that these individuals participate in treatment by expressing their preferences and making personal choices about their living conditions, work, and recreational activities. When environmental provisions are adequate and handled well, they may lead to an improved quality of life and a considerable reduction in maladaptive affective and behavioral symptoms. Environmental provisions for the child with an intellectually disabled parent require particular attention. A home program for an intellectually disabled person should provide access to preferred activities, present choices with regard to household tasks and community activities, and schedule highly preferred tasks and activities immediately after nonpreferred (but essential) tasks.

Educational Interventions/ Skill Development

A major challenge in the treatment of ID(IDD) is to foster the development of adaptive social skills. Emotional and behavioral disturbances are linked to poor self-regulation. Ideally, an educationally based program should focus on the social, communication, and vocational skills needed to improve self-control and reduce maladaptive behavior. Essential elements of a social skills program include independence training (teaching self-help and leisure skills), communication training (enhancing speech and nonverbal communication [e.g., signing, gesture, picture/word boards]), and self-management skill development (teaching strategies for self-monitoring and self-reinforcement). Social skills training provides specific and concrete instructions, introduces observation and modeling of effective behavior, structures reinforcement, and focuses on teaching through simple,

observable tasks. Successful social skills programs include demonstrations by instructors, modeling, role-playing, social practice, positive reinforcement, and constructive feedback. Training might include initial instruction and practice in a therapeutic environment, followed by practice in natural community settings to generalize the behavior.

Individual, Family, and Group Psychotherapy

Psychotherapeutic interventions, though shown to be effective in ID(IDD), are often underutilized because of skepticism regarding their effectiveness for intellectually disabled persons (Szymanski 1980). The goals of psychotherapeutic treatment include resolution of internalized conflict, improvement in self-esteem, and enhancement of personal competence and independence. A supportive, developmentally focused approach by the therapist utilizing shorter, more frequent sessions may be necessary. O'Hara (1999) provided a review of psychotherapy for persons with ID(IDD). Lynch (2004) suggests that for the adult, age-related issues, assistance with transition to community life, bereavement, and dealing with risks in the environment that may arise in community living are areas for psychotherapeutic intervention. The implementation of psychotherapy for intellectually disabled persons requires considerable flexibility and ingenuity on the part of the therapist because of the complexity of various disabling conditions.

Evidence Base for Psychotherapy: Outcomes Research

The research literature regarding outcomes of psychotherapeutic interventions in persons with ID(IDD) is limited (Dagnan 2007). It includes case studies and single-subject designs, as well as controlled comparisons and clinical trials. There is considerable variability in the kinds of outcome rating scales used. There are few randomized controlled trials.

Prout and Nowak-Drabik (2003) published a research review of psychotherapy effectiveness studies conducted over a 30-year period. Ninety-two of the studies reviewed were included in the analysis. In these studies psychotherapy was defined as including face-to-face therapy using established techniques. Studies were rated by an expert consensus panel and classified with regard to the nature of the research and the outcome and effectiveness domains. Some studies reviewed were limited in regard to methodological rigor and design. These included single-subject designs and case studies with poorly described interventions. The meta-analysis based on the 92 studies included in the analysis found a wide range of research designs, types of interventions, and participants. Expert consensus involved use of rating sheets, expert raters, and consensus and reliability measures. The authors in their analysis required that the therapist be qualified and knowledgeable in the use of these techniques. The focus of the treatment was on modifying feelings, values, attitudes, and behaviors. Change was rated on a scale from no significant change, to minimal change, to significant change. On the basis of these data, effect sizes were calculated. The authors concluded from their review that psychotherapy is "moderately" effective for individuals with ID(IDD) and yields a "moderate" amount of change across age groups, ID(IDD) severity level, techniques used, and theoretical approach. The authors concluded that psychotherapeutic interventions should be considered as part of overall treatment

plans for persons with ID(IDD) as individual interventions in practice and clinic settings.

Approach to Psychotherapy

The overall psychotherapeutic goals are as follows: 1) to improve adaptive functioning by helping the individual to master developmental tasks and avoid stigmatization; 2) to promote resiliency in the individual by enhancing his or her ability to cope with psychosocial stressors; and 3) to prevent the emergence of symptoms during key transitional times during development (e.g., adolescence) when new capacities emerge.

When initiating treatment, the psychotherapist must address the same basic issues that are addressed with typically developing persons. However, establishing therapeutic contact may require considerable initial effort. Such effort is essential because rapport is basic to enhancing motivation to change. As the psychotherapeutic process unfolds, the extent of communication deficits, as well as the patient's response to psychosocial stressors and the presence of co-occurring behavioral and psychiatric disorders, may become more evident. Consequently, the first phase of treatment also serves as an extended evaluation that may be used to develop a more comprehensive and realistic case formulation. In that phase, psychotherapy with developmentally disabled children and adolescents includes an educational component that involves teaching new adaptive skills.

In working with youths diagnosed with ID(IDD), it is important to work with parents or caregivers who can provide important collateral information regarding day-to-day functioning and interval history When parenting skills and rearing techniques are being taught, it is essential that parents and family members understand their role in encouraging and facilitating self-efficacy. Behavioral treatments must be coordinated with educational, communication science, occupational therapy, and medical services; social services; and services provided by other professionals. Group home or residential staff should be actively involved in establishing the psychotherapeutic goals.

Because multiple caregivers may be involved, interventions must be applied consistently across various settings to maintain gains across these settings. This is particularly true in the teaching of social skills. Because data gathered in one setting may require a change of program in others, communication across settings is vital. When new information comes up during psychotherapy that is pertinent to another treatment setting, there must be a means for that information to be conveyed. Finally, the psychotherapist should be prepared for long-term continuous treatment with episodic crisis management. The frequency of sessions will decrease as symptoms improve.

Adaptation of Psychotherapeutic Methods

Psychotherapeutic techniques need to be adapted for work with developmentally disabled persons. Hurley (1989) recommended six adaptations to psychotherapeutic techniques that she culled from multiple published reports: 1) matching the technique to the child's, adolescent's, or adult's cognitive and developmental level; 2) taking a directive approach; 3) maintaining flexibility in the choice of treatment methods; 4) involving family and staff; 5) recognizing one's own interpersonal distortions and biases; and 6) providing help in acknowledging the extent of the disability. Even though these

adaptations are based largely on case reports, they do offer reasonable general guidelines for clinical practice.

Matching the therapeutic intervention to the child's, adolescent's, or adult's cognitive and developmental level and type of disorder requires the use of syntactically simple language geared to the individual's developmental level and provision of concrete examples in an understandable context. The therapist must frequently verify that the intellectually disabled person has understood what has been said and repeat concepts from one session to the next until they are fully understood (Hurley and Hurley 1986). Hurley and Hurley (1987) suggested that clinicians who are working with older intellectually disabled persons should carefully build on the relationship as they would when working with younger children. Initial sessions may be used to help the patient discriminate and label feelings before work is done to link feelings to situations. A directive approach is needed to maintain the focus of the therapeutic interactions on pertinent issues. In the first session, the reason for the referral is clarified and a specific and concrete explanation is given about what therapy is, how often therapy sessions will occur, and what will take place in each session. The therapist must carefully explain the rules and structure for each therapy session. Firm but appropriate limits are established for aggressive, destructive, and excessively affectionate behavior in the session. When speaking with the intellectually disabled child, adolescent, or adult, the therapist must ask for minute particulars about events that have occurred and the person's responses to them. The therapist may recommend alternative means of coping with stressors and may provide alternative interpretations of life events. The person with ID(IDD) is encouraged to express curiosity and ask questions. This may be a new experience, because in the past he or she may not have been provided an opportunity to do so. When specific questions are posed, the therapist must consider answering them directly rather than exploring for fantasy material that may underlie them. Providing appropriate feedback for effective behavior and offering reassurance when successes are reported are crucial. Acknowledging potential doubts about handling tasks and problems and indicating that, in general, people are not always sure how to accomplish a task may be useful. Moreover, frequently reviewing alternative strategies to master a problem is one way to facilitate problem-solving ability and rational thinking.

Alternative approaches are often required when treatment is not progressing adequately. When selecting treatments and particular verbal and interpersonal play techniques, the therapist must take into account the child's cognitive, communicative, and affective developmental level. Play techniques must be adapted to the person's mental age; drawings, music, and puppets are generally used. The length and frequency of therapy sessions should be based on the person's ability to tolerate the designated length of time necessary for the therapy to be effective (Stavrakaki and Klein 1986). More frequent and briefer sessions often are necessary for developmentally disabled persons. Adaptability is particularly important to maintain continuity and establish a time perspective in crisis situations.

Persons with mild ID(IDD) may be very aware of negative interpersonal responses to them (Reiss and Benson 1984). Like other disabled persons, an intellectually disabled person suffers when learning that he or she is different and is stigmatized as a member of a devalued group.

The effect of the specific disability also must be addressed. Intellectually disabled persons often have not been targeted as a group who can benefit from disability counseling (Hurley 1989). Because the individual may not clearly understand the nature of his or her disability, specific problems arise in disability counseling. This is particularly true with ID(IDD), in which limitations in cognitive ability themselves limit insight and reasoning about the nature of the disability. Although an intellectually disabled person may have no clear-cut awareness of what "ID(IDD)" means, he or she may be sensitive to being labeled "retarded" (Szymanski and Rosefsky 1980). Such anxiety may be reduced by explaining that ID(IDD) refers to slowed development in some areas, especially academic areas, but that there may be strengths in other areas. However the disability is described, the explanation needs to be concrete and presented at the individual's developmental level. When discussing the specific disability, the therapist may ask the disabled person if he or she understands 1) the diagnostic label, 2) why he or she is in special classes, and 3) how his or her development differs from that of a sibling.

Along with disability counseling, the therapist may provide "ability" counseling by helping the person place his or her overall disability into perspective (Hurley 1989). For example, the individual might be taught that he or she is unique as a person—that he or she has value as a human being that is separate and distinct from being a disabled person, and that his or her abilities are important. Hurley (1989) suggested using the principles of rational-emotive therapy for children, adolescents, and adults with ID(IDD). In doing so, the therapist may need to confront the child or adolescent directly regarding his or her possible unwillingness to acknowledge or accept the limitations of ID(IDD) or other disabilities. Care must be taken if the therapist feels that he or she is "attacking" the patient's self-esteem when asking directly about limitations. The risk of encouraging autonomy is that the individual may be impulsive and, because of cognitive limitations, make choices that could have dangerous consequences. Therefore, the context in which the child or adolescent might make decisions outside of therapy must be carefully understood. Moreover, in developing choices, training in appropriate social assertiveness is needed.

When the therapist is considering the developmentally disabled person's ability to respond to and use interpretations about his or her behavior, the cognitive and linguistic capacity to talk about past events and to use autobiographical memory is critical. One must ask whether the individual has reached the stage of development at which theory of mind—the ability to anticipate the intentions and feelings of others and act based on these anticipations—is present (Thirion-Marissiaux and Nader-Grosbois 2008). To assess this degree of awareness, the therapist might ask questions such as "What might your mother have been feeling when you did that?" Those individuals who tend to benefit most from therapy have the capacity to recognize the similarity of their current life situations to previous life events. Such self-understanding may lead them to make different choices based on recognition of past maladaptive patterns of behavior.

Group Therapy

Group therapy is a particularly useful approach for the adolescent and adult age groups in persons with mild ID(IDD), more so than for younger children. In group therapy, the patient has an oppor-

tunity to directly practice social skills and learn how to develop supportive relationships. Adolescents and adults may feel more comfortable discussing peer-related topics in a group setting with others of their own age group who have similar disabilities. In the group, the therapist actively facilitates these interactions and provides structure. The support and reassurance of group members help individuals verbalize their concerns. Specific topic areas will arise in the group that may be further pursued in individual treatment sessions.

Family Interventions

In working with children with ID(IDD), the family and other caregivers require direct support. Individual and family therapy are often combined to provide consistency in management across settings. The family serves as a therapeutic setting for change and the consolidation of new skills. As therapy progresses, parents may ask for advice on parenting. The treatment goals are positive parenting skills and improved relationships with siblings. For the family, times of crisis include both when the initial diagnosis is received and subsequent phases of adaptation when feelings are mixed. If such feelings are not addressed, they may become chronic sorrow. Kanner (1953) observed that

> whenever parents are given an opportunity to express themselves, they invariably air their emotional involvements in the form of questions, utterances of guilt, open and sometimes impatient rebellion against destiny, stories of frantic search for causes, pathetic accounts of matrimonial dissensions about the child's condition, regret about the course that has been taken so far, anxious appraisals of the child's future, and tearful pleas for reassurance. (p. 375)

Families require support in identifying resources and need specific guidance in management and support techniques. Advocacy by the therapist in helping families in these ways is essential.

The family may become conflicted in coping with a developmentally disabled family member, and often marital discord may ensue. Commonly, maternal overinvolvement and paternal withdrawal from the therapy occur and must be addressed at the onset of treatment. If this does happen, couples therapy may be needed. Alternatively, a parent may need to be seen individually to work through his or her bereavement. When the disabled person becomes a source of displacement and scapegoating for other family issues, these issues are worked through in family therapy. Several psychological processes in dealing with parents who are adapting to the disabled child include phases of denial, projection, guilt, and dependency that must be recognized and worked through.

Family interview sessions may include the developmentally disabled person, and when they do, family interactional patterns should be observed as an additional source for diagnostic information. Family therapy may provide an avenue to support new capabilities for independent functioning. When adolescents are included, it may result in better family negotiating styles if conflict exists between the adolescent and the parent(s). Family treatment may foster assertiveness in the adolescent and may lead to better relationships with siblings, who are often stressed when a child or adolescent in the family has a developmental disorder.

Behavioral Interventions

Behaviorial therapies are the most commonly used and the best-studied treat-

ment approaches for behavior disorders in persons with ID(IDD) (Sturmey 2012). The techniques of *applied behavior analysis*, *behavior modification*, and *contingency management* are included in these therapies. Behavioral procedures are effective for maladaptive patterns of behavior that are the result of faulty learning and for emotional and behavioral symptoms linked to pathophysiological disorders. Behavioral treatments are used to enhance adaptive, socially desirable behavior; to reduce maladaptive behavior; and to promote habilitative skills. Behavioral interventions may be specifically indicated for self-injurious behavior, self-stimulatory behavior, aggressive behavior, and habit training and are used most effectively for people with mild-moderate to severe-profound levels of ID(IDD).

Cognitive-behavioral therapy (CBT) is used most commonly for persons with milder forms of ID(IDD). There are two general approaches: self-management and cognitive therapy for distorted thinking. *Self-management* is based on the assumption that emotional and behavioral problems are the consequence of a lack of cognitive skills. CBT is a package of behavioral interventions that include self-monitoring, self-control methods, problem solving and decision making, exposure therapy, and anger management. Relaxation training, skills acquisition, and social skills training are incorporated into the treatment program. These approaches have been most useful for improving anger management and improving self-esteem (Rose et al. 2000). Cognitive therapy also deals with cognitive distortions, which may take the form of abnormal beliefs and inappropriate attributions or inferences about others' actions. Such distortions may be a consequence of irrational emotions. Treatment examines the person's understanding of the meaning of his or her experiences. Self-awareness and social awareness are required for this approach to be effective, so use of cognitive therapy is reserved primarily for individuals with mild ID(IDD).

Pharmacotherapy

Psychotropic medication can be an important adjunct to psychosocial interventions and behavioral therapies in the treatment of intellectually disabled persons with mental disorders. Drug treatment is initiated following careful assessment, and typically targets co-occurring conditions for which pharmacotherapy is a first-line indicated treatment. Before drug treatment is begun, it is particularly important to do a baseline assessment of movement and behavior, in addition to the routine medical testing (e.g., blood tests, electrocardiogram). Consent for medication treatment (or assent in cases where individuals have a legal guardian for medical decision making) must always be obtained. Careful follow-up for side effects is especially important, because many intellectually disabled persons may not be able to provide self-report of drug-related symptoms.

An international consensus conference was held to establish recommendations for the use of psychotropic medications in intellectually disabled persons with psychiatric disorders, and the recommendations have been published as a handbook (Reiss and Aman 1998). Aman et al. (2004) provide updated guidelines following the consensus conference based on questions to experts about first-line, second-line, and third-line medication choices for various diagnostic indications. The Health Care Financing Administration (1997) manual *Psychopharmacological Medications—Safety Precautions for Persons With Developmental Disabilities* may be consulted by surveyors seeking

to determine whether a facility is in compliance with regulations for psychotropic drug use in persons with ID(IDD). Finally, the World Psychiatric Association Section on Psychiatry of Intellectual Disability has developed an evidence- and consensus-based guide for practitioners regarding the use of psychotropic medications for problem behaviors (Deb et al. 2009). These guidelines include discussions of formulation, initiation of treatment, assessment of outcomes and adverse effects, follow-up arrangements, and discontinuation of medication.

In the United Kingdom a series of systematic reviews has been conducted for each major class of psychotropic medication use in persons with ID(IDD) (Deb et al. 2008; Sohanpal et al. 2007; Sturmey 2012; Unwin and Deb 2011). Such reviews are essential because the history of excessive use of typical antipsychotics, such as chlorpromazine and thioridazine, in residential settings in the past has led to consideration and caution in prescribing psychotropic medication among professionals working with persons with ID(IDD) and co-occurring psychiatric conditions. The reviews are modeled after the National Institute of Clinical Excellence Guidelines (NICE).

Antipsychotics

The review to determine the evidence base for the effectiveness of antipsychotics (Unwin and Deb 2011) focused on randomized clinical trials (RCTs) with risperidone, the only atypical antipsychotic for which randomized trial data were available. Risperidone was significantly more effective than placebo in managing problem behaviors but was associated with risk-associated adverse effects, primarily somnolence and weight gain. Tardive dyskinesia has long been a concern with typical antipsychotics. Although not reported in this systematic review, other authors (Fodstad et al. 2010; Matson et al. 2010) have found tardive dyskinesia associated with atypical antipsychotics in people with ID(IDD) diagnoses. Older persons are at greater risk for these symptoms, but children and adolescents with long-term use are also at risk.

Before prescribing medication for behavior management, the clinician should assess the causes and consequences of behavior and consider all medication and nonmedication-based options. For example, behavioral treatment often can be effective. Randomized controlled trials (RCTs) are needed. For example, in one RCT comparing risperidone, haloperidol, and placebo in the treatment of aggressive behavior in patients with ID(IDD), aggression decreased in all three groups, but the greatest reduction and the best outcomes were seen in the placebo group (Tyrer et al. 2008).

Mood Stabilizers

The review to determine the evidence base for the effectiveness of mood stabilizers in the management of behavior problems focused on adults who satisfied strict inclusion criteria (Deb et al. 2008). A randomized trial of lithium use and two non-RCTs, one on lithium and the other on carbamazepine, were included. The evidence supports the use of lithium and antiepileptic mood stabilizer medication for behavior management in adults with ID(IDD). Most studies reviewed had methodological flaws, so the authors advise caution in interpreting these results (Deb et al. 2008).

Antidepressants

The review to determine the evidence base for the effectiveness of antidepressants (Sohanpal et al. 2007) identified one

crossover randomized controlled trial in a small cohort. Seven prospective uncontrolled trials and two retrospective studies were identified. Nine studies focused on selective serotonin reuptake inhibitors (SSRIs), and one focused on the tricyclic antidepressant clomipramine. Despite small numbers of participants, frequently nonvalidated outcome measures, and short period of follow-up, the evidence suggests that antidepressants, especially SSRIs, reduced aggression and self-injurious behavior, but in less than 50% of the persons enrolled. The effects were greater with co-occurring anxiety or a concurrent diagnosis of obsessive-compulsive disorder. The study authors highlighted concerns regarding adverse effects (Sohanpal et al. 2007).

Stimulants and Clonidine

Rowles and Findling (2010), in their review of pharmacotherapy options for the treatment of ADHD and ADHD-like symptoms in children and adolescents with neurodevelopmental disorders, discussed methylphenidate, the most extensively studied drug (Handen et al. 1991, 1999); clonidine; and amphetamines. The review included ADHD treatment in children with a known neurodevelopmental syndrome, such as fragile X syndrome and fetal alcohol spectrum disorder, in which attention deficits and hyperactivity are well recognized. There is evidence for improvement in children with neurodevelopmental disorders and ADHD, but not to the same degree as in typically developing children with ADHD, with the difference probably related to the type of underlying brain dysfunction. Other studies have focused on preschool children with ADHD diagnoses, with similar findings of improvement and increased side effects (Ghuman et al. 2009).

Electroconvulsive Therapy

Thuppal and Fink (1999) reported that electroconvulsive therapy (ECT) can be effective in intellectually disabled adults but should be used only in those whose depression does not respond to several trials of antidepressant medication. However, ECT is controversial and is rarely used; there are difficulties with consent, and there may be a perceived concern about abuse (Szymanski and King 1999).

Conclusion

Ongoing efforts are being made to improve mental health treatment for persons with ID(IDD) diagnoses. The literature on psychotherapy, behavioral treatments, and psychopharmacological treatments has grown substantially in recent years. There is a need for more focused psychotherapy studies with flexibility in design that takes into account a developmental perspective, utilize attachment models, and consider mastery motivational approaches. Early recognition is needed to provide early interventions. Prospective studies are also needed. Therapist characteristics, the importance of family support, and adherence to practice parameters are important. Better, more valid outcome measures are needed.

Considerable progress is being made in the psychopharmacological treatment of behavioral and psychiatric disorders. Psychopharmacological research leads to new hypotheses, and as new drugs become available for treatment, these hypotheses are being explored. More rigorous application of appropriate experimental design in the evaluation of drug efficacy is needed. When successfully applied, findings from new research may lead to less polypharmacy and a

more rational approach to drug treatment and reduction in side effects.

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CHAPTER 2

Communication Disorders

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Communication is a process by which information is exchanged between individuals through a common system of symbols, signs, or behavior. *Language* is the systematic means of communicating ideas or feelings by the use of conventionalized signs, sounds, gestures, or marks having understood meanings. The emergence of communication skills in the developing child is necessary for human socialization (Gemelli 1996); likewise, the development of appropriate verbal language skills and its production (speech) are critical for adaptive competence (Wiener and Dulcan 2004). Impairments in speech or language in childhood are often associated with deficits in other areas of functioning, such as academics and developmental competencies (Beitchman et al. 1996), as well as emotional health (Conti-Ramsden and Botting 2008).

Systems of Classification

The American Speech-Language-Hearing Association (ASHA) has defined *communication disorder* as "an impairment in the ability to receive, send, process, and comprehend concepts or verbal, nonverbal and graphic symbol systems" (Block et al. 1993). ASHA further divides this category into disorders of speech and language, whereby *speech disorder* is defined as "an impairment of the articulation of speech sounds, fluency and/or voice," and *language disorder* is defined as "impaired comprehension and/or use of spoken, written and/or other symbol systems" (Block et al. 1993). Language disorders are noted to involve three specific areas of interest: language form (pho-

nology, morphology, and syntax), content (semantics), and function (pragmatics). These noted areas can occur in any combination (Block et al. 1993).

DSM-5 (American Psychiatric Association 2013) classifies communication disorders in much the same fashion (Table 2–1), similarly drawing distinctions between speech disorders (speech sound disorder and childhood-onset fluency disorder [stuttering]) and language disorders of syntax and semantics (language disorder) or pragmatics (social [pragmatic] communication disorder). The diagnosis unspecified communication disorder can be used when full criteria for any specific communication disorder are not met and the clinician chooses not to specify the reason, or when insufficient information is available to delineate a specific diagnosis. This is a restructuring from the previous edition, DSM-IV-TR (American Psychiatric Association 2000), which took an approach of focusing on speech production and content (phonological disorder and stuttering), expressive language (expressive language disorder), and language comprehension (mixed receptive-expressive language disorder).

TABLE 2–1. DSM-5 communication disorders

Language disorder
Speech sound disorder
Childhood-onset fluency disorder (stuttering)
Social (pragmatic) communication disorder
Unspecified communication disorder

The *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision (ICD-10; World Health Organization 1992), classifies communication disorders as specific developmental disorders of speech and language, making distinctions between speech disorders (specific speech articulation disorder) and disorders of language expression (expressive language disorder) and reception (receptive language disorder).

Communication disorders also have received specific classification from the federal government through the Individuals With Disabilities Education Act (IDEA). The Individuals With Disabilities Education Act (2004) defines *speech or language impairment* as "a communication disorder, such as stuttering, impaired articulation, a language impairment, or a voice impairment, that adversely affects a child's educational performance." This brief definition is in line with the other classification systems discussed (ASHA, DSM, and ICD) and provides a basis upon which children may become eligible for services in the educational system. For example, 46% of those children ages 3 through 5 (2004) and 19% of those students ages 6 through 21 (2005) served under the Part B program of IDEA were categorized as having speech or language impairments (U.S. Department of Education 2010).

Comorbidity

During early childhood, speech and language are exquisitely interlinked in both their emergence and their development (Gemelli 1996). Along with this high degree of parallel and developmental continuity between normal speech and language, there is a high rate of comorbidity among the speech and language disorders (Grigorenko 2007). In children with normal cognitive functioning, the rate of comorbid speech and language disorders is between 11% and 15% (Shriberg et al. 1999). There is also a substantial co-occur-

rence with learning disorders (Hallahan et al. 1996). For example, language disorders and speech sound disorders are often associated with reading disorder (American Academy of Child and Adolescent Psychiatry 1998).

Communication disorders also carry an increased risk for psychiatric disorders and other emotional and behavioral problems. In 1986, Beitchman and colleagues examined the prevalence of psychiatric disorders in children with speech and language disorders. Their research confirmed a high rate of psychiatric disorders (48.7%) in young children with speech and language impairments, with attention-deficit disorder accounting for the largest percentage (30.4%) of any psychiatric disorder. Beitchman et al. have also examined longitudinal psychiatric outcome at follow-ups of 7 years (Beitchman et al. 1994) and 14 years (Beitchman et al. 2001) with an initial cohort of children age 5 years. At the 7-year follow-up in 1996, children who had a speech and language impairment at age 5 were more likely to have a psychiatric diagnosis, specifically an emotional disorder, regardless of current speech and language disorder status. At the 14-year follow-up, children who had a speech and language impairment at age 5 had higher rates of psychiatric diagnoses; specifically, anxiety disorders and antisocial personality disorder occurred at significantly higher rates. A meta-analysis by Benner et al. (2002) indicated that approximately three of four (71%) children formally identified with emotional and behavioral disorders had clinically significant language deficits and approximately one of two (57%) children with diagnosed language deficits were identified as also having emotional and behavioral disorders. Overall, early language disorders are risk indicators for concurrent and future psychiatric problems, with a prognostic preference for emotional, anxiety, and behavioral disorders (Toppelberg and Shapiro 2000).

Assessment

Although language and learning disorders are common, they remain underdiagnosed in community and psychiatric settings (Beitchman et al. 2001). Problems related to language are among the most common reasons for clinical presentation in children ages 3–16 years, regardless of psychiatric diagnosis (Toppelberg and Shapiro 2000). Therefore, mental health clinicians need to have a basic understanding of the normal developmental variance and age-appropriate competencies in language development. Specifically, clinicians should have a working knowledge of language dimensions, including comprehension/production, vocabulary/grammatical complexity, and retardation/deviance (Shapiro 1982).

The clinical diagnostic interview is an initial opportunity to begin the process of assessment for a suspected language or speech disorder. The assessment should include first and foremost a detailed chronological history of symptoms. Parental report and collateral records from the child's school or pediatrician offer important enhancement to the office-based clinical assessments of cognitive skills (American Academy of Child and Adolescent Psychiatry 1998). Most formal language assessments are limited in the range of skills measured; therefore, the clinical evaluation remains crucial because it can help to quantify and qualify the child's ability to communicate effectively in real-life settings (Toppelberg and Shapiro 2000). If a language or speech disorder is suspected following initial assessment, basic psychoeducational testing is warranted. Although the requirement of a substantial discrepancy

between cognitive and language functioning obtained from standardized measures is no longer necessary for diagnosing a language disorder according to DSM-5 (American Psychiatric Association 2013), testing can help to direct the need for more in-depth assessment or referral to a speech-language pathologist (American Academy of Child and Adolescent Psychiatry 1998).

Other potential contributors to delays in speech and language development include deafness or significant hearing loss, intellectual disability, autism spectrum disorder, other psychiatric disorders, organically based communication disorders (e.g., cleft palate, cerebral palsy, acquired childhood aphasia), and disorders associated with maternal substance abuse or maltreatment (Martin and Volkmar 2007). Further assessment, such as audiometric testing (Sadock and Sadock 2007) or a pediatric or neurological evaluation for cerebral palsy or other organic neurological impairments affecting speech, should be considered.

Treatment

General Considerations

Communication disorders are generally treated by speech-language pathologists; however, a multimodal treatment approach is considered the standard. This approach typically involves referral of the child to the appropriate treatment provider (i.e., speech-language pathologist) and involvement of the educational system where the child is enrolled (American Academy of Child and Adolescent Psychiatry 1998). In general, treatment interventions for speech and language disorders focus on functional improvement. Treatment interventions should be based on the individual's presentation and tailored to his or her specific needs and symptoms. Depending on the disorder, specific exercises can be employed to improve speech impediments, voice quality, oral motor control, and fluency. Additional techniques can be used to improve word comprehension, word recall, listening comprehension, and sentence formulation. In cases where pragmatic language abilities are not developed, the therapist can use behavioral therapies to help the patient learn the skills needed for social communication, such as the understanding of nonverbal cues.

The mental health clinician's role should remain integral in the overall treatment of communication disorders. Assessment and treatment of comorbid psychiatric conditions are critical to the overall success of any interventions for speech and language disorders. The mental health clinician can also provide an educational and supportive role for parent and child. Importantly, the mental health clinician acts as a liaison between the educational system, family, and other treatment providers to assist in planning the child's individualized education program (IEP) and in determining proper classroom interventions and placement (American Academy of Child and Adolescent Psychiatry 1998).

Specific Disorders

Language Disorder

Language disorders are currently conceptualized in the literature using multiple classification systems. The current discussion will present the information concerning treatment based on the domains of language development, expression, and understanding/comprehension (reception). DSM-5 has established language disorder as a single diagnostic category to identify children with persistent

difficulties in the acquisition and use of language (language delay) with evident deficits in production (expression) and comprehension (reception) functions (Box 2–1).

Box 2–1. DSM-5 Diagnostic Criteria for Language Disorder

315.32 (F80.2)

A. Persistent difficulties in the acquisition and use of language across modalities (i.e., spoken, written, sign language, or other) due to deficits in comprehension or production that include the following:
   1. Reduced vocabulary (word knowledge and use).
   2. Limited sentence structure (ability to put words and word endings together to form sentences based on the rules of grammar and morphology).
   3. Impairments in discourse (ability to use vocabulary and connect sentences to explain or describe a topic or series of events or have a conversation).

B. Language abilities are substantially and quantifiably below those expected for age, resulting in functional limitations in effective communication, social participation, academic achievement, or occupational performance, individually or in any combination.

C. Onset of symptoms is in the early developmental period.

D. The difficulties are not attributable to hearing or other sensory impairment, motor dysfunction, or another medical or neurological condition and are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

Delays in language emergence and its use (expression) are frequent developmental problems, with reported prevalences ranging from 2.3% to 19% in children ages 2–7 years (Buschmann et al. 2009; Cable and Domsch 2011; McLaughlin 2011). Children with difficulties in both the expression and reception of language constitute a smaller portion of those with a language disorder. Prevalence rates vary with age, with up to 5% of preschoolers and 3% of school-age children being affected (American Psychiatric Association 2000).

As with all of the communication disorders, intervention is typically administered by the speech-language pathologist. A common model that most speech-language pathologists practice is based on the notion of *naturalness* (i.e., resembling "real life"). This model can be seen as a continuum from the most natural child-based interventions (daily activities and facilitated play) to the least natural, totally clinic-based interventions (drills, drill play, and clinician-directed modeling). The most likely approach, however, is a hybrid model including milieu therapy, focused simulation, and script therapy (Paul 2007). The deployment of treatment interventions can also be described as being either direct or indirect/mediated. A *direct* intervention is delivered by a speech-language pathologist working directly with a child in a clinical setting. An *indirect/mediated* intervention is delivered by a child's parent or primary caregiver or the child's educational provider (teacher, classroom aide, etc.) with coaching or supervision by a speech-language pathologist (Sadock and Sadock 2007).

Clinical controversy exists regarding whether to provide language intervention for children younger than 5 years. There are two schools of thought: 1) pro-

vide treatment as soon as deficits are identified, or 2) hold off until the child is preschool age (commonly known as the "wait and see" approach) (Sadock and Sadock 2007). Current research suggests that intervention is effective for the 2- to 3-year-old child with language delay (Buschmann et al. 2009; Cable and Domsch 2011). Children up to age 3 years are likely to do well with play-based therapy that encourages communication using language. Preschoolers and school-age children can find benefit from individual or group setting therapy that focuses on more individualized language needs (vocabulary, sentence structure, conversational discourse, etc.) and builds on the children's natural development (Sharp and Hillenbrand 2008). Direct and indirect therapy interventions are equally effective overall for children with speech and language delays (Allen and Marshall 2011; Law et al. 2003).

For both late language emergence and expressive language difficulties, interventions can be directly administered by a speech-language pathologist or indirectly delivered by a trained parent or educational provider. Preschool-age children optimally benefit from interventions that promote social communication and literacy along with oral language use. Kindergarten age children benefit from additional teaching of prereading skills, and young children benefit from achieving rudimentary reading skills (Sadock and Sadock 2007). Direct and indirect therapy interventions are equally effective overall in children with receptive language difficulties, but the overall effect is smaller than that for delays in language emergence and use (Law et al. 2003).

Speech Sound Disorder

Speech disorders have typically been examined by separating dysfunction of speech into the areas of production of speech sounds (phonology) and speech fluency (stuttering). Speech sound disorders include problems with articulation (making sounds) and phonological processes (sound patterns). Speech fluency disorder is a disturbance in the normal fluency and time patterning of a child's speech. DSM-5 has developed a new categorical formulation for speech disorders and has established two diagnostic categories: speech sound disorder (Box 2–2) and childhood-onset fluency disorder (stuttering) (see Box 2–3 in the next subsection). In DSM-IV, these diagnostic categories were represented by phonological disorder and stuttering, respectively.

Box 2–2. DSM-5 Diagnostic Criteria for Speech Sound Disorder

315.39 (F80.0)

A. Persistent difficulty with speech sound production that interferes with speech intelligibility or prevents verbal communication of messages.
B. The disturbance causes limitations in effective communication that interfere with social participation, academic achievement, or occupational performance, individually or in any combination.
C. Onset of symptoms is in the early developmental period.
D. The difficulties are not attributable to congenital or acquired conditions, such as cerebral palsy, cleft palate, deafness or hearing loss, traumatic brain injury, or other medical or neurological conditions.

Phonological disorders are among the most prevalent speech disorders, affecting 10% of combined preschool- and school-age populations (National Institute on Deafness and Other Communication Disorders 1994). The essence of this type of speech disorder is a failure to use developmentally age-appropriate speech sounds, in the absence of a congenital or acquired condition (American Psychiatric Association 2013). Characteristics of this type of speech disorder include omissions, additions, distortions, and substitutions. An *omission* is when a speaker does not produce certain sounds, syllables, or classes of sounds, whereas an *addition* is when a speaker adds an extra sound to a word. A *distortion* occurs when a child changes a sound slightly from its correct form (as in a lisp), and a *substitution* is when a child exchanges one sound for another in a word (e.g., saying *wat* instead of *rat*) (Sadock and Sadock 2007).

Treatment of phonological disorders begins with a speech pathologist's careful analysis of symptomatic speech patterns. The clinical assessment includes recognition of sounds that are being misarticulated, as well as understanding of the "pattern and underlying rules by which the child's phonology is organized" (Van Riper and Erickson 1996, p. 228). Once the particular child's phonological disorder is defined, a plan involving specific techniques to target deficiencies can be developed. The overall goals of any therapy are to improve the child's amount of intelligible speech and to achieve more effective communication with others (Gierut 1998). Throughout the years, different therapies have been developed to target phonological disorders. Two of the more basic modes of intervention are behavioral approaches and linguistic approaches.

A *behavioral approach* uses operant conditioning to modify a child's language. In a method identified as progressive approximation or shaping, the clinician starts with repeating the sound error made by the child, then making a series of transitional sounds until the standard sound is produced. The child then slowly goes through the series of transitional sounds and is rewarded for correct modifications. This technique has been shown to help children learn the correct way to produce sounds (Van Riper and Erickson 1996). A *linguistic approach* to phonological disorder therapy helps children understand the proper rules of the spoken language and recognize distinctive features of sounds that they omit or replace. The goal of this approach is to encourage the child to discard errors by learning how erroneous language affects the interpretation of his or her speech by others (Blache and Parsons 1980).

Alternatively, a more traditional approach to providing therapy to a child with a phonological disorder, the *linguistics approach,* takes into consideration both the speech production (behavioral) aspects and the complexity of spoken language (linguistic aspects) required for effective communication (Van Riper and Erickson 1996). This treatment approach is used to help children recognize their speech sound errors and then to correct and strengthen their ability to produce the correct sound. With this approach the child first learns how to produce the desired target sound, usually through imitation of the speech-language pathologist's modeling. Then the child learns to produce the desired sound in conjunction with different syllables, then words, phrases, and sentences. This process of increasing the complexity of utterances using the target sound culminates in the correct use of the sound in conversational speech (Gierut 1998).

Another method to treat phonological disorders is the *minimal pair* treatment.

This treatment focuses on how changes in a single sound (e.g., the beginning sounds in *b*at and *c*at) can alter the meaning of the words (Gierut 1998). With this approach, the child is taught how two paired words (a minimal pair) differ and learns to identify and contrast the words (through definitions or picture cards). The goal is for the child to recognize the need to produce the differing sound for each word to communicate different meanings. This treatment ends when the child correctly uses the words in communication situations both inside and outside therapy (Blache and Parsons 1980). The minimal pair approach is a form of sound teaching and is frequently used in the treatment of phonological disorders related to presumed cognitive or linguistic difficulties (Gierut 1998).

The transition of a new and corrected sound from the therapy environment to everyday speech can also present unique challenges. Certain techniques can help encourage the child to monitor his or her own language. One technique is to include daily speech assignments involving monitoring of language errors by self or others. For example, a parent can be assigned to assess the child's language errors while they talk about the child's day at school. Alternatively, the child can be asked to carry around a card and make a tally mark whenever he or she utters an error. Lastly, encouraging the child to monitor his or her language based on proprioceptive feedback has been shown to help automatize new sounds. To do this, the child wears headphones to block out the sound of his or her voice, and speaks words with the target sound. By focusing on the movements of the mouth and tongue while uttering the sound correctly, the child is able to develop motor memory (Van Riper and Erickson 1996).

Childhood-Onset Fluency Disorder (Stuttering)

Stuttering is a speech disorder best described as a disruption in fluent and age-appropriate verbal expression (Box 2–3). This dysfluency of speech is characterized by a variety of disruptive actions and may be accompanied by associated behaviors or mannerisms. The disruptive actions of stuttering can include speech rate disturbances, sound prolongations, and repetition in specific sounds, syllables, words, or phrases. Associated behaviors that may accompany severe presentations of stuttering include eye blinking, facial grimacing, and abnormal head or body movements (Block et al. 1993; Sadock and Sadock 2007). Stuttering has a prevalence of 1% in young children and affects boys at a rate three times greater than girls. The typical onset for this disorder is between ages 2 and 7 years, with onset occurring by age 6 in 80%–90% of children (American Psychiatric Association 2013). It is estimated that up to 75% of preschoolers who stutter will spontaneously recover within 4 years. The children who are more likely to spontaneously recover are girls whose stutter onset was very early and who have stuttered less than 1 year. Boys with a later stuttering onset in addition to delayed speech and language development have a less favorable outcome (Prins and Ingham 2009). Children whose symptoms do not spontaneously remit will typically progress to more serious symptoms and associated behaviors (Prasse and Kikano 2008).

Box 2–3. DSM-5 Diagnostic Criteria for Childhood-Onset Fluency Disorder (Stuttering)

315.35 (F80.81)

A. Disturbances in the normal fluency and time patterning of speech that are inappropriate for the individual's age and language skills, persist over time, and are characterized by frequent and marked occurrences of one (or more) of the following:
   1. Sound and syllable repetitions.
   2. Sound prolongations of consonants as well as vowels.
   3. Broken words (e.g., pauses within a word).
   4. Audible or silent blocking (filled or unfilled pauses in speech).
   5. Circumlocutions (word substitutions to avoid problematic words).
   6. Words produced with an excess of physical tension.
   7. Monosyllabic whole-word repetitions (e.g., "I-I-I-I see him").

B. The disturbance causes anxiety about speaking or limitations in effective communication, social participation, or academic or occupational performance, individually or in any combination.

C. The onset of symptoms is in the early developmental period. (**Note:** Later-onset cases are diagnosed as 307.0 [F98.5] adult-onset fluency disorder.)

D. The disturbance is not attributable to a speech-motor or sensory deficit, dysfluency associated with neurological insult (e.g., stroke, tumor, trauma), or another medical condition and is not better explained by another mental disorder.

The treatment of stuttering begins with a thorough assessment of the child's specific stuttering behaviors, as well as an evaluation of consequent abilities and dysfunction, such as general communication skills, ability to meet educational goals, and interactions with others (Yaruss et al. 2012). As with the other communication disorders, this detailed clinical assessment should be performed by a speech-language pathologist. The treatment of stuttering can be challenging because of the lack of evidence-based consensus about therapy. The focus of current treatment methods for stuttering is on management of stuttering events and symptom reduction, as opposed to elimination (Prasse and Kikano 2008). Current treatment approaches can be categorized into one of two areas: fluency shaping or stuttering management (Prins and Ingham 2009). Therapeutic programs for stuttering can also be described as direct and indirect therapies, as discussed previously in the section on language disorder treatments.

Fluency shaping and stuttering management are behavioral management approaches to the treatment of stuttering. *Fluency shaping* generally consists of changing one's speech pattern by self-management, after learning prolonged speech strategies. The techniques involved in producing prolonged speech can include rate reduction, gentle and unstressed onset of speech, division of speech to accompany single breaths, and deliberate smooth flow between sounds and words (Prins and Ingham 2009; Sadock and Sadock 2007). When the child is first learning to control speech, the rate of production will be much slower than typical speech, with short phrases and sentences. Over time, the child will produce smooth speech at faster rates, in longer sentences, and in more challenging contexts until speech sounds are both fluent and natural. In *stuttering management,* or stuttering

modification, the stutterer is taught to react to his or her fluency disruptions in a calm manner and not express previously associated behaviors, mannerisms, or discomforts. The goal is to have speech free of unnecessary effort or reactions, although it will be dysfluent at times (Prins and Ingham 2009). Fluency shaping and stuttering management can be viewed as *direct* therapy interventions because these techniques are typically learned and practiced with a speech-language pathologist. It is also important to note that they are not mutually exclusive and are often used together (Yaruss et al. 2012).

Indirect therapies for stuttering typically involve manipulation of the child's environment to support the development and maintenance of fluency outside the clinician's office. One well-established indirect therapy is Parent-Child Interaction Therapy, an approach that helps preschool- to school-age children and their parents to shape the environments needed for the children to correct their speech habits (Millard et al. 2008). This technique is based on the idea that stuttering is a multifactorial disorder and influenced by the child's speech and language abilities, physiological ability to correctly produce sounds, environmental influences on speech, and psychological and emotional influences on speech (Smith and Kelly 1997; Starkweather and Gottwald 1990). By targeting parents as well as the individual child, this technique helps in shaping the environment so that the parent and child interact in ways that can facilitate fluency and decrease negative emotions associated with speech (Rustin et al. 1996). The parents are taught to spend a set amount of time with the child, analyzing, influencing, and correcting their child's speech. Clinic hours are spent monitoring this interaction and augmenting what is being done for a better result. During the first 6 weeks of this training, the child's fluency increases drastically. This initial period is followed by the consolidation period, lasting for another 6 weeks, during which parents continue to work with the child. Studies show that if parents spend less time with the child during this period, regression may occur (Rustin et al. 1996).

An example of a combined therapeutic program is the Lidcombe Program, which targets children up to age 6 years. It uses predominantly indirect therapy, in that the clinician trains the parent to use operant conditioning to shape the child's fluency. During everyday speech situations, the parent praises the child for passages of fluent speech and draws supportive attention to stuttering. When the child stutters, the parent asks the child to repeat the phrase without stuttering and then praises the child when this is done successfully (Goodhue et al. 2010).

In addition to techniques and schedules developed for decreasing stuttering, specific counseling therapies have been developed to help people who stutter cope with their fears and change their dysfunctional thinking patterns. Responses to each type of therapy are very individualized; therefore, the therapist must individualize the approach to each patient. Each of these therapies can be used either as stand-alone therapy or to enhance other stuttering techniques that the clinician puts into place. Examples of these therapies that can be used to treat stuttering include personal construct therapy, transactional analysis, rational emotive therapy, solution-focused brief therapy, and neurolinguistic programming (Ward 2006).

Social (Pragmatic) Communication Disorder

Another area of language that has received special attention and has been a

continuing area of debate is social communication. Since at least the 1980s, children who exhibited an inability to use language appropriately in a social context have been identified as having a unique and possibly separate phenotype (Toppelberg and Shapiro 2000). These children's difficulties with the *pragmatic* aspects of language may occur with or without any significant structural (semantic) difficulties (Bishop and Norbury 2002).

Research in this area has been complicated by the fact that children who exhibit pragmatic difficulties have often been classified as having pervasive developmental disorders and, indeed, often share features of impaired social communication (Whitehouse et al 2009). Pragmatic language impairment has, until recently, been difficult to research effectively due to lack of clear diagnostic criteria (Bishop and Norbury 2002). More recently, continuing research has further delineated a population of children who have primary pragmatic difficulties but do not exhibit or develop severe social deficits and repetitive behaviors that could otherwise be characterized as autism spectrum disorder (Mandy et al 2011; Whitehouse et al. 2009). These children who have problems with understanding and engaging in socially appropriate discourse are now classified in DSM-5 as having social (pragmatic) communication disorder (Box 2–4).

Box 2–4. DSM-5 Diagnostic Criteria for Social (Pragmatic) Communication Disorder

315.39 (F80.89)

A. Persistent difficulties in the social use of verbal and nonverbal communication as manifested by all of the following:
   1. Deficits in using communication for social purposes, such as greeting and sharing information, in a manner that is appropriate for the social context.
   2. Impairment of the ability to change communication to match context or the needs of the listener, such as speaking differently in a classroom than on a playground, talking differently to a child than to an adult, and avoiding use of overly formal language.
   3. Difficulties following rules for conversation and storytelling, such as taking turns in conversation, rephrasing when misunderstood, and knowing how to use verbal and nonverbal signals to regulate interaction.
   4. Difficulties understanding what is not explicitly stated (e.g., making inferences) and nonliteral or ambiguous meanings of language (e.g., idioms, humor, metaphors, multiple meanings that depend on the context for interpretation).

B. The deficits result in functional limitations in effective communication, social participation, social relationships, academic achievement, or occupational performance, individually or in combination.

C. The onset of the symptoms is in the early developmental period (but deficits may not become fully manifest until social communication demands exceed limited capacities).

D. The symptoms are not attributable to another medical or neurological condition or to low abilities in the domains of word structure and grammar, and are not better explained by autism spectrum disorder, intellectual disability (intellectual developmental disorder), global developmental delay, or another mental disorder.

Because social (pragmatic) communication disorder is a relatively new diagnostic category, treatment modalities for this disorder need to be examined using the previous nonformalized constructs, which include pragmatic language impairment and semantic-pragmatic disorder. As for the other language disorders, treatment is primarily provided using a combination of both direct and indirect treatment methods, under the guidance of a speech-language pathologist. Treatment of pragmatic language impairment can use both direct approaches to target impairments in language use and indirect approaches to support learning and personal development in areas of impairment relevant to conversational speech and understanding of social context (Adams et al. 2006).

Recent research has attempted to identify evidence-based treatment approaches to address pragmatic language impairment. In an evidence-based review of current treatments, Gerber et al. (2012) were unable to identify any specific treatment modalities that they could recommend in addition to standard clinical practice. They concluded that further investigation is needed to support any individual treatment approach to social communication behaviors and pragmatic language skills. Of note, barriers to making any evidence-based treatment recommendations included the lack of a large number of available studies to review and the paucity of standardized ways to measure treatment goals in this heterogeneous patient population (Gerber et al. 2012).

Although research of specific treatments for social communication impairments has yet to yield evidence-based interventions, promising study results have been published that examine an intensive manualized social communication intervention. This research, by Adams et al. (2012), implemented an intensive manual-based intervention that provided individualized interventions for children aimed at remediation of semantic language impairments and pragmatic difficulties, as well as training for social interactions and social cue interpretation. Children with social communication impairments were compared with children with similar impairments who received treatment as usual following standard speech-language pathology interventions. The authors concluded that their manualized intervention did provide some significant treatment effects, as demonstrated by parent-reported improvement in the children's pragmatic functioning and social communication and teacher-reported improvement in the children's classroom learning skills.

Conclusion

The various assessments and treatment methods used to provide standard care for individuals with communication disorders in clinical, educational, and home settings are typically delivered under the direct care, supervision, or supportive training of a speech-language pathologist. However, the mental health clinician can provide an invaluable service as part of the multidisciplinary team, because the co-occurrence of various psychiatric disorders and other emotional and behavioral problems is common in children with communication disorders. The underdiagnosis of speech and language disorders in both community and psychiatric settings, as well as their comorbidity with other mental health disorders, emphasize the need for mental health providers to be familiar with and knowledgeable in the area of communication disorders. The role of the mental health care provider can go

beyond that of providing treatment for specific mental health issues to include the provision of supportive and educational assistance to the child and family. It is equally important for the mental health clinician to be available as a liaison to the educational system and to advocate for the appropriate use of available school-based services. This multimodal approach to treatment is critical to the overall success of any individualized treatment plan for a child with a communication disorder.

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CHAPTER 3

Autism Spectrum Disorder

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This chapter is intended to provide the reader with an up-to-date understanding of treatment outcome studies on autism spectrum disorder (ASD). The focus is on highlighting the findings and methods of several key research reviews and meta-analytic outcome studies that have been carried out since 2000. The main purpose of this chapter is to inform the reader about what treatment outcomes have been studied and what this body of work means for best practices in evidence-based treatment for ASD.

This chapter is aimed at the professional who is not a specialist in ASD treatment or research but who needs to understand what has been studied, what has been learned, and how strong the evidence is for a particular practice. The approach in this chapter is intended to support the practitioner who needs to tailor treatment for a patient with ASD who is of a specific age, functional level, and symptom profile. To this end, the chapter refers to research reviews (listed in Table 3–1) rather than citing many specific studies; the reader is thereby directed to detailed expert resources without having to go directly to primary studies, because primary research cannot tell the reader what is regarded as "best practice." The discussion of key methodological and epistemological issues and controversies is designed to aid the practitioner in 1) troubleshooting services that may be lacking in fidelity to the research on a treatment model and 2) modifying treatments that are developmentally inappropriate even though evidence-based practices seem to be followed.

Since 2000, a number of meta-analyses and comprehensive reviews of the literature have been conducted from different perspectives (e.g., educational, behavioral, developmental) to weigh which treatments have been rigorously researched to support so-called best practice. The first consensus document of this

TABLE 3–1. Key meta-analytic reports of autism treatment research outcomes

Study authors	Literature studied	Focus/conclusions
National Research Council, Committee on Educational Interventions for Children With Autism (2001)	Empirical outcome studies supporting treatments for young children with autism	Recommended ≥25 hours of services for early intervention.
Rogers and Vismara (2008)	Comprehensive evidence-based treatments (1998–2006) with group design or single-subject multiple baseline designs, for subjects ages 3–5 years	Deemed Lovaas's treatment "well established." Concluded that more research needed for treatments rated "possibly efficacious" because fewer studies reported.
Wilczynski et al. 2009 National Standards Report (National Autism Center)	Educational and behavioral autism treatment literature (1957–2007); subjects to age 22 years	Identified 11 established interventions. Specified treatment by age, diagnostic group, and treatment targets.
Odom et al. (2010a)	Thirty comprehensive treatment models based on six domains	Reported that largest number of CTMs used applied behavior analysis methods.
Young et al. 2010 IMPAQ International Centers for Medicare and Medicaid Services	Behavioral and psychosocial interventions from birth to adulthood (studies dated 1998–2008)	Found that majority of interventions are for children. Concluded that more research is necessary for transitioning youth and adults.
Warren et al. 2011 Agency for Healthcare Research and Quality	Behavioral, educational, medical, allied health, complementary, and alternative medicine; subjects ages 2–12 years	Noted that few studies have compared among manualized CTMs (e.g., Early Start Denver Model, Lovaas) or reported impact of responder characteristics on treatment outcomes.
Odom et al. (2010b)	Instructional practices or strategies with outcome measures, experimental control, and gains; subjects to age 22 years	Identified 24 focused intervention practices in the classroom that met criteria for evidence-based interventions.

Note. CTM=comprehensive treatment methods.

nature was written by the National Research Council's Committee on Educational Interventions for Children With Autism in 2001. More recent reviews, such as the National Autism Center's National Standards Report (Wilczynski et al. 2009), the final report of IMPAQ International Centers for Medicare and Medicaid Services (Young et al. 2010), and the Agency for Healthcare Research and Quality's Comparative Effectiveness Review (Warren et al. 2011), describe basic meta-analyses to identify which treatments are considered to be or are still emerging as evidence-based interventions. Table 3–1 provides a summary of these core reports, which are cited throughout this chapter. The interested reader can read these reports to investigate the details, find references for specific studies examined, and obtain more information about the treatment methodologies of specific studies. Autism psychopharmacology is addressed separately from these studies in a section toward the end of this chapter.

The final section of this chapter, "DSM-IV to DSM-5: Diagnostic and Treatment Implications," presents the DSM-5 criteria for ASD (American Psychiatric Association 2013) and considers whether these new criteria may result in cases having the same or different diagnoses than they would have using DSM-IV-TR criteria (American Psychiatric Association 2000). The emphasis in that discussion is on what identifying and labeling cases differently in the two nosologies may mean for interpretation of research conducted on samples using DSM-IV criteria (American Psychiatric Association 1994) and for treatment of patients in samples based on DSM-5 diagnoses. This is important because essentially all the research reviewed here was carried out on DSM-IV samples.

Core Issues in Research on Autism Spectrum Disorder

Developmentally Appropriate Curriculum

The consensus is that for all treatments for ASD, programs must be developmentally appropriate (National Research Council 2001). Children with ASD who have significant developmental delays have lower current functioning than typical for their chronological age, and therefore the curriculum they are taught (adaptive behavior, language skills, social skills, or academic subjects) must be adjusted downward to be developmentally appropriate. ASD treatments have been best studied in children under age 5 years. For this age group, the consensus is that the combination of interventions used must be intensive, lasting at least 20–25 hours per week, and that parental involvement can and should effectively extend the child's educational time through incidental teaching and by promoting generalization of directly taught material to daily activities. Studies of treatment outcomes beyond the early intervention years have more often focused on training communication and social skills, and positive outcomes for such research have been most consistently obtained in samples of subjects with "higher-functioning autism," commonly defined as those with IQs greater than 70.

Comprehensive Versus Focused Treatment

In any review of autism treatment, it is helpful and conventional to identify in-

terventions as either 1) comprehensive treatment methods (CTMs) or 2) focused interventions (FIs). CTMs often contain a cluster of FIs, and a given FI may be used by multiple CTMs. Any given CTM or FI may be aimed at reducing maladaptive behavior that is incompatible with learning, or promoting developmentally expected change, or both. In any of the three cases, a CTM or FI will hypothesize a decrease in severity of one or more specific symptoms of ASD. (Treatments that have no a priori hypothesis to be symptom specific but rather are anticipated to globally help autism usually turn out to be ineffective; see the section "Non-Evidence-Based Treatments.")

Methodology Versus Curriculum Content

Both methodology (how a skill is taught or trained) and curriculum (what is being taught or trained) can be expected to affect outcome. If a method is applied with high fidelity but teaches a skill for which the child lacks prerequisites, the efficacy of a method may be underestimated. If a high-fidelity method is used *and* the curriculum is developmentally appropriate, a more strongly positive outcome should be expected and can be characterized as best practice.

Behavioral Change Outcome Studies

Much autism treatment outcome research prior to 2000 focused on demonstrating the efficacy of behavioral treatment methods influenced by the work of Lovaas (1987), who had asserted that almost half of autism cases could achieve "recovery" with his specific applied behavioral analysis (ABA) protocol, discrete trial training (DTT). Lovaas's rates of recovery have not been replicated on unselected populations, although further research has shown that, indeed, a smaller number of children who receive initial behavioral treatments may no longer have presentations that meet criteria for ASD by the teen years (Fein et al. 2013).

Anyone prescribing an autism treatment needs to clearly indicate what the treatment is intended to target and not merely to state, for example, that the child "needs applied behavior analysis (ABA) because he has ASD." If the goal is to reduce self-injurious behavior or another behavior incompatible with instruction (e.g., inattention, lack of reward response), the behavior can be addressed with ABA. However, the prescriber needs to ensure that curriculum is included in the ABA program to address the behavior. (ABA is described more fully in the next section of this chapter.) Notably, treatments that eschew behavioral or developmental methods to change maladaptive behaviors or promote developmental goals (e.g., facilitated communication; see Wilczynski et al. 2009) have failed to yield empirically demonstrable positive outcomes.

Effective early interventions aimed at establishing learning readiness skills such as attention, compliance, and imitation are taught using behavioral methodologies. Evidence for the effectiveness of behavioral methods for developing learning readiness exists primarily for toddlers and preschoolers, who are at the age at which developing learning readiness usually commences and behavioral excesses due to communication frustration have not yet emerged. Behavioral methods for reducing other more atypical maladaptive behaviors (e.g., self-injurious behaviors) have been best studied in ASD samples in the middle childhood through teen years.

Developmental Growth Outcomes

After initial learning readiness has been established through ABA programs, most children with ASD transition into interventions aimed at promoting developmental growth. Most of them begin tapering off or leaving ABA programs to move partly or fully into school-based services between ages 3 and 5 years. Limited evidence exists for the differential efficacy for ABA as a primary mode of intervention in ASD beyond the early elementary years. School-age children with ASD may receive intervention in individual or group settings, and in special day class or mainstream settings. As discussed by Warren et al. (2011), the benefits of inclusion have been best studied and efficacy has been best demonstrated in higher-functioning children who have successfully "graduated" from ABA programs.

Defining Evidence-Based Practice

There are tiers of evidence in reaching conclusions that are likely to be replicable and that therefore constitute evidence-based practice (EBP). Ideas for EBP in ASD have grown from theory or research in related fields, such as behaviorism, child development, psycholinguistics, or neuroscience.

Single-Case Designs

The field of ABA has a tradition of methodologies practice derived from single-case studies in which response to intervention is monitored, modified, and documented. A successful case can be replicated using the same method, and over time this practice can demonstrate whether a given treatment approach can be generally useful to change a given behavior. Discrete trials and the recording of their data continue to be used in ABA-based treatments even after the methods and treatment content become quite standardized. In the practice of ABA, continuously recorded data from an individual case can be used to empirically modify aspects of methodology, such as frequency and degree of prompting, use of reinforcers, and reinforcement schedules. The field of ABA generally rejects the alternative idea of gathering periodic evaluative data (e.g., from quizzes and tests) to modify curriculum—the widespread practice in education—which is considered by proponents of ABA to be less precise. In contrast, ABA's single-case methods remain anathema to many psychological and educational researchers trained in the tradition of experimental and quasi-experimental group methods. Antipathy between these groups is fairly widespread. Of the reports listed in Table 3–1, only the National Standards Report (Wilczynski et al. 2009), written largely by and for behavior analysts, gives equal weight to findings established through single-case designs.

Quasi-Experimental Studies and Evidence-Based Practice in Autism

The largest proportion of studies supporting current EBP in ASD comprises quasi-experimental studies. Such work compares two or more groups: an experimental group plus controls or comparison subjects. A control group is one that ideally receives nothing that can be construed as an "active ingredient" targeting the outcome, but in reality few studies achieve this ideal. A relatively powerful approach in ASD outcome research has become the waiting-list control group;

however, a family with a child in this group, once recruited to a study of a particular outcome, becomes aware that the outcome is desirable and may find other ways to move toward that outcome. Even in randomized controlled trials (RCTs), considered the gold standard for autism treatment, waiting-list control subjects are seldom likely to be as "clean" as they are in medical double-blind RCTs in which randomized subjects begin receiving either treatment or placebo as soon as selected. Because feasibility of well-controlled randomized trials is low and cost is high, quasi-experimental studies of outcomes in ASD often compare the experimental condition to treatment as usual (i.e., the community standard) while controlling for known and powerful independent variables.

Limitations of empirical studies often include 1) lack of sufficient sample size to evaluate individual differences (e.g., for whom it works best), 2) lack of control for unstudied independent variables (e.g., treatment in university lab, prior treatment history), 3) lack of evidence that gains on the study's outcome measures translate into functional gains, and 4) lack of follow-up to validate that gains were sustained. Some threats to validity can be addressed by using varied samples, community settings, varying outcome measures, and longitudinal methodologies.

Implementing Evidence-Based Practice in Autism Research

Other concerns in moving from research to EBP include manualization, training, and establishing fidelity to the research model, important because CTMs are often developed in university settings and may not carry over readily to community settings (e.g., the Early Start Denver Model for Young Children With Autism; Rogers and Dawson 2010). For example, ABA-DTT, the single most widely disseminated autism CTM, has three levels of treatment administrators: 1) behavior analysts, 2) case managers who train line staff and update plans of behavior analysts, and 3) line staff who carry out the bulk of direct service. Some autism CTMs, such as Floortime-DIR (Greenspan and Weider 1998), are more child-centric in that intervention consists of following the child's lead and/or expanding the child's repertoire. This makes the curriculum much harder to standardize and evaluate compared with ABA-based programs. Another issue is that with the mandate for intensive treatment, community treatment implementers are often paraprofessionals with associate's or bachelor's degrees, and fidelity to the treatment model risks being poor if training and monitoring are not of high quality.

Applied Behavior Analysis for Autism Spectrum Disorder

Applied Behavior Analysis Methods

Because ABA has become such a large part of evidence-based practice in ASD, and because many physicians and mental health professionals in the position to prescribe treatment for ASD have relatively little background in principles of ABA, some of the fundamentals will be reviewed here. More focused behavioral interventions often result from a "functional behavioral analysis," which begins with an examination of the ABCs—the

antecedents and *consequences* of either a *maladaptive behavior* that needs to be reduced in frequency or an *adaptive behavior* that is to be increased in frequency. Change is then sought through one or more of these methods:

- *Prompting*—Moving the subject toward a goal, often physically, until prompts can be gradually removed (through prompt fading).
- *Reinforcement*—Providing a scheduled incentive (a rewarding food, sensory, or social contingency) when desired behavior is achieved.
- *Chaining*—Either stepwise building of a desired behavior (forward chaining) or stepwise elimination of an undesired behavior (backward chaining).
- *Differential reinforcement of other or incompatible behavior*—Reducing an undesired behavior or increasing a desired behavior by reinforcing other behavior (e.g., reinforcing a child for pointing a finger rather than hitting) or an incompatible behavior (e.g., reinforcing a child for keeping hands in pockets instead of flapping hands). Related concepts are *response interruption* and *redirection.*
- *Extinction*—Ignoring an undesired behavior while preventing reinforcing consequences from occurring (e.g., ignoring screaming, as a behavior associated with the consequence of getting a need met).

These FI methods of ABA are most often administered in an "error-free" learning paradigm—that is, adjusted in such a way that small enough incremental steps ensure success while preventing failure. Prompting and reinforcement are not decreased until mastery (often about 80%) is achieved. These ABA-FI methods are comprehensively applied to teach a group of skills needed for development or to maintain conditions that allow the subject to be available to instruction; the aggregation of these methods make up an ABA-CTM.

Discrete Trial Training

The best-known, most widely used ABA-CTM is DTT. DTT involves mostly one-to-one teaching, first of learning readiness skills such as attention, compliance, and imitation, and then chronological age-appropriate concepts (e.g., receptive identification of body parts) or, if also carried out with a developmental curriculum (better), teaching developmentally (e.g., looking or pointing to request—which developmentally precedes oral requesting).

Applied Behavior Analysis as Evidence-Based Practice for Autism Spectrum Disorder

The use of both behavioral and developmental approaches for about 25 hours per week for preschool-age children has become the most widely adopted standard (e.g., National Research Council 2001). The use of Lovaas's method of ABA-DTT led to improvements in IQ, nonverbal IQ, language, and adaptive skills (see Wilczynski et al. 2009). Subsequently, treatments for children in both one-to-one and group settings, in which both purely behavioral and developmental teaching were used, have been found effective across a number of studies (Warren et al. 2011; Young et al. 2010).

Rogers and Vismara (2008), in a study of children under age 5, added to this work by reviewing studies on responder characteristics. Across studies, one-to-

one instruction is more effective than parent training alone, and both together are likely most effective.

Pivotal Response Training

Pivotal response training (PRT), a more naturalistic model for an ABA-CTM, lends itself to intervention during teachable moments when the child wants or needs something, or when a differential reinforcement (choice) situation can be set up (Schreibman and Koegel 1996). PRT is built on DTT, but in PRT, behavior is reinforced not by an external reinforcer (e.g., food) but instead by the child's desire to obtain a preferred choice. Other ABA-FIs are incorporated, such as shaping and chaining as in DTT. PRT was designed to reduce prompt dependency and to promote generalization and spontaneity (i.e., to initiate through communicating choice). DTT has been criticized for being overly adult initiated, for using unrelated reinforcers (e.g., getting a candy for identifying a cat), and for being too structured, thereby leaving treated children with fewer opportunities to develop self-initiation or curiosity. PRT is more readily implemented by parents at home than is DTT, and it capitalizes on the child's self-initiative and curiosity. Parent training programs are often associated with administration of PRT, providing parents with skills to facilitate their child's social and communication skills needed for daily activities. A high-quality practice would be to use PRT to structure parent-child interactions combined with DTT for direct teaching.

Other Applied Behavior Analysis Interventions

Positive behavioral supports is an ABA-CTM that incorporates a number of ABA-FIs to differentially reinforce desired behavior (e.g., an intermittent schedule to maintain an emerging or desired behavior, such as by occasionally saying, "I like how you are staying in your seat; here's a token"). This approach emphasizes shaping and reinforcing positive behavior as a differential reinforcement of other, and has been particularly effective when rates of maladaptive behavior are low and developmental gains are targeted outcomes, such as in classrooms.

Functional communication training involves differential reinforcement of increasingly advanced communication paired with positive behavioral supports. This training is typically incorporated into behaviorally based group learning for younger subjects with ASD.

Self-management is related to functional communication training for older and higher-functioning individuals. The individual is taught to self-administer a preplanned reinforcement schedule to promote behavior change in one or more areas.

Naturalistic Interventions

The term *naturalistic interventions* can refer to ABA approaches such as PRT, but more often the term is associated with child-centric CTMs such as the Hanen method for communication training (Prizant and Wetherby 1998) and Floortime-DIR (Greenspan and Weider 1998). Like PRT, these naturalistic interventions can focus teaching on opportunities that occur in the child's day; getting needs met, obtaining a preferred activity or item, and having a choice in continuation or termination of an activity are all leveraged as motivators. Although there is strong empirical support for PRT as EBP, many fewer studies have been reported of these other more child-centric naturalistic methods; the difference may be due to the fact that the latter are harder to

standardize, as discussed earlier in the section "Core Issues in Research on Autism Spectrum Disorder." Also, naturalistic interventions require a greater understanding of the child's repertoire than ABA-DTT line staff typically have, making it harder to disseminate the interventions beyond parent training paradigms. Nevertheless, these methods hold substantial promise with respect to enhancing learning, especially when a child is home with his or her parents. Naturalistic teaching strategies can incorporate parents, caregivers, relatives, teachers, siblings, and peers in any setting where they interact with the child. Naturalistic teaching strategies have been demonstrated to increase imitation skills, pretend play skills, and joint attention in young children, which translate into social gains across settings.

Evidence-Based Practice Targeting Specific Symptom Domains

Behavioral Change

EBPs aimed at change in maladaptive behaviors are well supported using ABA-FIs, as discussed earlier in the section "Applied Behavior Analysis for Autism Spectrum Disorder." The term *functional behavior analysis,* or FBA, refers to the analysis of the "ABCs" (antecedents, behavior, consequences) to which selected ABA-FIs are applied. Other methods with good empirical support for managing behavior include 1) visual supports (pictures to enhance comprehension of spoken or written words), 2) picture schedules (pictures used to order activity), and 3) visual schedules (pictures that depict steps of a task and otherwise support transitions or choices). These visual accommodations can be particularly efficacious at response prevention of undesired behaviors (for the best review of this body of work, see Wilczynski et al. 2009).

Communication Interventions

Some interventions for children with ASD have focused on promotion of communication skills. All of the reviews cited in Table 3–1 cover some aspects of communication or language development. For preverbal and nonverbal children, the Picture Exchange Communication System (PECS; Howlin et al. 2007), which involves exchanging a card with a photo or icon to receive the depicted object or activity, has had an impact on social development as well, because it allows the child to communicate with others. Related methods can result in an increase in generalized requesting and, when used in collaboration with social skills training, an increase in duration and frequency of social interaction. There has been less direct investigation of augmentative and alternative communication devices such as iPad apps that have many of the same cognitive supports as PECS but more salient and motivational graphic support. Older augmentative and alternative communication devices such as the DynaVox are being supplanted by iPads, which are more amenable to personalized (and therefore more motivating) content.

For older children and those at the stage of speaking in sentences, "scripting"—providing the child with a script for dialogue for specific interactions—has shown success in enhancing social competence. Research has used both written scripts and audiotaped scripts. Scripting and then script fading can lead

to increased use of scripted statements and, then, to an increase in unscripted statements.

Social Skills Development

Deficits in social competence are a core symptom domain in ASD and have the greatest specificity in delineating ASD from other childhood neurodevelopmental disorders (Odom et al. 2010a, 2010b; Warren et al. 2011; Young et al. 2010). Several interventions have shown a positive impact on directly promoting interpersonal skills, some mediated by decreasing maladaptive behaviors or by increasing communication. Efforts to increase social competence have been directed at 1) simple behavior change, 2) development of affective understanding (e.g., reading faces), and 3) improved social cognition (e.g., increasing perspective taking and theory of mind). Direct teaching of social skills includes shaping joint attention skills (a prerequisite to social interaction), teaching conversational initiative such as greeting others, and modeling skills used to initiate play with others. Affective understanding approaches include strategies for recognizing emotional states in self and others, such as social stories, prediction of storylines from books or children's movies, and acting classes. The goal of social skills interventions is to increase social cognition to lead to improved theory of mind, increased social problem-solving skills, and affective self-regulation.

In choosing a treatment to address social competence, as in skill development in other domains, consideration of the child's developmental level is key. Early interventions for very young children typically focus on working within the parent-child dyad. Joint attention interventions in working with young children highlight response to social cues, initiating social interactions, and regulating interactions. Several of the joint attention interventions involve the parent. Dependent variables include focusing on faces, turn-taking, initiating, and responding to joint attention bids (see Rogers and Vismara 2008). Interventions for preschool-age children typically concentrate on peer play, affective understanding, and the reciprocal nature of social relationships. The focus for slightly older children is on supporting prosocial behavior and encouraging social play.

Social competence interventions for older school-age children and adolescents typically aim to enhance perspective-taking skills, improve problem solving, and increase overall social cognition. Modeling interventions encourage children with ASD to imitate behavior demonstrated by another and can increase play skills. Learning via video self-monitoring appears to increase unprompted social engagement in classrooms.

Peer training or peer-mediated interventions are also supported as EBP for social development. These interventions involve teaching typically developing peers effective ways to facilitate appropriate play and social interactions, as well as academics, with children with ASD.

Social narratives (e.g., "Social Stories" is a manualized version; Nichols et al. 2005) and other story-based strategies have been shown to decrease inappropriate behavior and to positively impact the development of social skills. These interventions use pictures and/or written narratives to describe social situations in detail and the expected social behaviors represented in them. Social Stories typically are short and concise in nature. Stories have been themed to encourage appropriate interactive play, conversation, and resolution of social difficulties.

Less research has been done on social competence interventions with transitional-age youth and adults. For individuals with more severe ASD, some evidence suggests the effectiveness of supported employment, structured teaching, and schedules to promote social adaptation. Cognitive-behavioral therapy (CBT) is an emerging treatment for higher-functioning and older subjects with ASD; CBT aims to change negative thought patterns and behaviors, and to increase positive emotions. CBT can support increased initiative in positive interactions with peers, help in developing more appropriate social problem-solving skills, and increase understanding of affective experiences. Teachers have reported generalization of CBT benefits, including increases in assertiveness, cooperation, and self-control.

Across all age groups, research on social skills in children with ASD has often been carried out in samples of high-functioning subjects with ASD because social skills are often the core deficit area. Generalization of these findings to younger and lower-functioning subjects who also have significant maladaptive behavior and communication deficits is questionable, because most of these interventions cannot be carried out with fidelity, let alone systematically evaluated for efficacy. A key concern in most social skills outcome research is the lack of follow-up data on persistence or generalization of social competence gains across settings.

Academic Skills Development

The goals for development of academic skills in children with ASD are either habilitation or accommodation. Habilitative programs are those used with the youngest subjects with ASD to put in place skills that will bring a child to a level at which that child can access the core curriculum for age-mates. Accommodations are intervention methods that involve using modified means to achieve academic goals. There is no clear distinction between what are accepted as EBPs in academic settings and what are behavioral or neurodevelopmental interventions offered outside school settings. Indeed, there is considerable overlap; for example, ABA-FIs such as self-management and token systems are often used to achieve academic outcomes. Of the reviews listed in Table 3–1, those by Odom et al. (2010b) and Warren et al. (2011) are most germane to studies made in school settings.

Techniques developed in ASD-specific milieus specifically for children with stronger visual than verbal skills are often used to habilitate or accommodate autism-specific learning deficits. The most widely disseminated CTM is the Treatment and Education of Autistic and Communication Related Handicapped Children (TEACCH) curriculum (Mesibov et al. 2005). TEACCH pioneered the first visual supports. This curriculum includes FIs such as activity schedules, picture schedules, and visual schedules, which were discussed earlier in the section "Applied Behavior Analysis for Autism Spectrum Disorder." Specifically, the program includes visual aids, individualized communication systems, self-care skills training, and daily living skills training.

Some ABA-CTMs are more focused on skill development in academic settings where children with ASD have the opportunity to learn from typically developing peers. Two specific programs, Walden Early Childhood Program (McGee et al. 2001) and Learning Experiences: An Alternative Program for Preschoolers and Parents (Strain and Hoyson 2000), have

demonstrated promising results for play and generalization of other skills. The Early Start Denver Model (ESDM; Rogers and Dawson 2010), mentioned earlier in the section "Core Issues in Research on Autism Spectrum Disorder," is a more integrated approach that borrows from many EBPs. ESDM is intensive, with 15 hours per week of one-on-one instruction; encourages parental involvement; and provides support in the home and in community settings. ESDM, which has good preliminary support, focuses on activities that become naturally reinforcing through a variety of developmentally appropriate tasks, based on the child's and family's preferences, to address a child's cognitive, communication, and social skills. The Floortime model, referred to in earlier sections of the chapter, involves developmentally based play, as does ESDM, but does not have an ABA-PRT-adult-led orientation. DIR involves three components: 1) functional emotional development; 2) individual differences in sensory modulation, processing, and motor planning; 3) and relationships and interactions. Unlike ABA-CTMs, the Floortime method (Greenspan and Weider 1998) does not focus on specific skills, but rather supports interaction by following the child's lead to establish engagement with activities intended to be playful, spontaneous, and creative. This approach alone has less empirical support than it does when combined with ABA elements, but it has strong theoretical support in programming for infants and toddlers.

Non-Evidence-Based Treatments

Alternative methods to traditional behavioral, developmental, or medication therapies have become popular adjunctive treatments for children with autism. Some parents react adversely to the precepts of structured behavioral interventions, which can be diametrically opposed to more laissez-faire or liberal methods of child rearing. Some parents regard homeopathy as necessarily more benign than allopathy and look to supplements rather than substances approved by the U.S. Food and Drug Administration (FDA). Internet marketing of nonmainstream treatments is prominent, whereas autism Web pages on EBPs sponsored by the National Institutes of Health or Centers for Disease Control and Prevention are relatively harder to find and contain more ambiguous advice than a commercial Web site.

For parents, lack of efficacy data or false claims of efficacy are largely indistinguishable from what an experienced clinician or researcher might consider a promising new intervention that has not yet been subject to much investigation. Frequently, parents of newly diagnosed children with ASD do not know that some non-evidenced-based treatments (e.g., various diets and nutritional supplements) have long been available but still have only testimonial support and are empirically unproven. Furthermore, parents may be biased to attributing their child's improvements to these self-initiated, self-monitored non-EBPs, rather than to EBPs, because non-EBPs are mostly self-funded rather than supported by public agencies or third-party payers. Clinicians working with parents who might pursue unsupported treatments can provide psychoeducation about placebo effects through techniques such as 1) encouraging hypothesizing of expected benefits beforehand; 2) suggesting strategies such as having a close relative, teacher, or therapist remain blind to the intervention; and 3) having parents and others write down their per-

ceived changes independently before sharing them.

Although most EBPs are theory based and then subjected to empirical study, there are other autism treatments that have not emerged from an evidence basis or that are supported by post-hoc theory (e.g., the leaky gut theory, vaccine toxicity, behavioral food allergies). These latter treatments of hypothesized autism-related problems mostly emerged from incidental observations (e.g., that taking secretin or maintaining a diet free of gluten and casein successfully treated leaky guts, which was then purported to somehow "cure" aspects of autism symptoms). The post-hoc theories tend to have weak explanatory power; for example, asserting that vaccines cause autism is tricky in a widely vaccinated population in which both positive and negative cases are vaccinated. Nevertheless, new "findings" are "published" on the Internet quickly and are easily accessed because of having had many "hits," as well as being found on Web sites with well-meaning names such as "Defeat Autism Now." Parents are unlikely to be able to distinguish these theories from bona fide findings that have appeared in peer-reviewed journals. In fact, the non-EBP findings are arguably more accessible because they do not involve entry through portals such as PubMed or use confusing technical language not understood by the lay reader.

A few specific non-EBPs warrant special attention, because parents often view these as research based and may ask a non-ASD specialist, such as a pediatrician, general psychiatrist, or psychologist, to "prescribe" them as part of their child's treatment plan. Of the reports in Table 3–1, those by Warren et al. (2011), Wilczynski et al. (2009), and Young et al. (2010) are good resources to review these in more detail. *Auditory integration training* protocols generally aim to address children's hypersensitivity to sound via listening to preferred music paired with exposure to increasing sound intensity. The stated goals are to improve auditory reception, lower sensitivity to sound, and improve focus, but research during the last 20 years has failed to support the efficacy of any auditory integration training approach. Similar to auditory integration training, *sensory integration* is based on the concept that the brain's response to sensory input needs to be "normalized" before higher-order processing can proceed efficiently. To this end, occupational therapists often provide weighted vests, deep tissue massage, brushing, and swinging; however, despite 35 years of practice, such procedures have not been empirically supported.

Like sensory integration and auditory integration training, *music therapy* for ASD is founded on the theory that children will be more engaged when listening to music than when listening to normal speech (perhaps because music is less social and communicative). As with sensory integration, the children may enjoy some of the activities, but clearly enjoyment alone is not indicative of efficacy. Music therapy has been studied with mixed reviews. More research is necessary before it can be considered an established intervention; it may be differentially effective when used with children with greater musicality, or when used in combination with pivotal behavioral approaches when music can be an intrinsic reinforcer.

Other interventions include animal therapies and physical interventions such as exercise and massage therapy. Animal therapies—the most extreme being dolphin therapy, but more typically horseback riding (hippotherapy) and therapy dogs—have been used to address cognitive, social, and psychological domains for children with ASD. Although animal-assisted therapy may be helpful for indi-

vidual children, there are likely individual differences, and these therapies present difficulties in parsing effects because the child is usually receiving more comprehensive treatments at the same time. Hyperbaric oxygen therapy, an expensive treatment more commonly used to treat decompression sickness in scuba divers, has undergone some study, but there is minimal confirmatory research, according to Warren et al. (2011). Warren et al. also noted that the popular gluten- and casein-free diet not only lacks efficacy but might confer nutritional deficit.

Psychopharmacology Research on Autism Spectrum Disorder

This chapter has focused primarily on behavioral, developmental, and educational treatments for ASD because these constitute the bulk of techniques for ameliorative intervention. Psychopharmacology should not be considered an initial or primary modality of intervention. Medication generally is considered only after behavior incompatible with instruction is not reduced via developmental progress or behavioral strategies alone. The youngest children with ASD have rapidly developing brains, and the long-term impact of approved (or off-label) psychopharmacological agents on the formation of neural circuitry is poorly understood. Therefore, the widely accepted clinical standard is to avoid medicating children under ages 5–7 years as a first line of treatment. Psychopharmacological agents have been developed to treat certain symptoms or symptom clusters in ASD rather than autism itself. Much of the psychopharmacology used in patients with ASD focuses on decreasing problematic behavior (aggression, tantrums, self-injurious behavior), hyperactivity and inattention, and stereotypical and repetitive behaviors. Much less research is available on psychopharmacology for core social or communicative deficits in ASD, which appear significantly more refractory to medication. Relatively few medications have ASD indications; psychopharmacology for ASD not uncommonly involves off-label use based on experience of the prescribing clinician.

Aggression and Self-Injurious Behavior

Aggression and self-injurious behavior symptoms in children with ASD have been addressed with typical and atypical antipsychotics. Many of these agents produce significant adverse side effects such as increased irritability, sedation, and—with older agents such as haloperidol—risk of dyskinesias. Currently, the newer atypical antipsychotics risperidone and aripiprazole are approved by the FDA to treat severe behavioral issues in ASD. Benefits of atypical antipsychotics were well demonstrated by the multicenter Research Units on Pediatric Psychopharmacology (RUPP) Autism Network (2005b), the single most important empirical project in autism psychopharmacology to date.

The RUPP Autism Network carried out the first double-blind, placebo-controlled study of risperidone for ASD and reported significant decreases in irritability, decreases in self-injurious behaviors, and benefit on the Clinical Global Impression Scale. However, side effects of risperidone included weight gain, fatigue, increased appetite, and drooling. A RUPP study involving a parent-training component and risperidone validated a synergistic effect, emphasizing that in

ASD, as in other childhood neurodevelopmental disorders, medication plus behavioral treatment is likely to produce the most positive results. Similar results have been obtained for olanzapine (another atypical antipsychotic), although this medication was associated with a higher side-effect profile. As with the selective serotonin reuptake inhibitors (SSRIs) in ASD, there are individual differences in benefit and side effects across the atypical antipsychotics (for review, see Canitano and Scandurra 2011).

Hyperactivity and Inattention

Symptoms of hyperactivity and inattention in ASD do not necessarily show the same medication responsiveness as in attention-deficit/hyperactivity disorder (ADHD), possibly because they are etiologically more multifactorial. Research on ADHD symptoms in ASD has been complicated in the past because DSM-IV restricted the comorbid diagnoses of ADHD and a pervasive developmental disorder, although that restriction has been removed in DSM-5, and preliminary work suggests substantial comorbidity. The earliest research on stimulant treatment in children with autism showed little effectiveness, and side effects included increased irritability, hyperactivity, stereotypies, and a loss of appetite. However, subsequent RUPP studies, including double-blind placebo trials, found that methylphenidate was effective in decreasing these same symptoms, as assessed by parents and teachers (Research Units on Pediatric Psychopharmacology [RUPP] Autism Network 2005a). Clonidine also has demonstrated some effectiveness in addressing hyperactivity and inattention. Guanfacine, which is possibly less sedating than clonidine, has demonstrated some effectiveness, may decrease autonomic arousal, and may have a more positive response in patients who do not have intellectual disability or who have poor response to stimulants. Atomoxetine has showed similar promise. A few limited studies suggest that antiepileptic mood stabilizers may also reduce symptoms of inattention and hyperactivity (Canitano and Scandurra 2011).

Stereotypic and Repetitive Behavior

Some medications target interfering stereotypic and repetitive behavior in ASD; these include SSRIs, atypical antipsychotics, and anticonvulsants. Studies by the Autism Treatment Network have shown that fluvoxamine, an SSRI, decreases repetitive thoughts, repetitive behaviors, maladaptive behaviors, aggression, and inappropriate repetitive language with only minor side effects (nausea and sedation). Citalopram, another SSRI, has also been used but with less efficacy. In addition to there likely being individual differences in responses, there is some evidence that SSRIs may be less effective and less well tolerated in younger prepubertal children than in adolescents and adults with ASD (Research Units on Pediatric Psychopharmacology [RUPP] Autism Network 2005b).

Stereotyped and repetitive behaviors in ASD have also been treated with antipsychotics and anticonvulsants. The atypical antipsychotic risperidone has been shown to significantly decrease stereotypical and repetitive behaviors. Anticonvulsants used in children with ASD and epilepsy show some benefit as mood stabilizers and may also decrease stereotypic and repetitive behaviors (specifically divalproex), although evidence is still tenuous.

Social Impairment

Social impairment, a core symptom of ASD, is receiving increasing attention in the psychopharmacology literature. Many studies of medications aiming to treat other target behaviors have also decreased social impairment, resulting in, for example, less active avoidance and less aggression. It is still not clear, however, whether reported social improvements (e.g., increased social interest) should be considered a main effect of any psychopharmacological treatment or a "halo effect" of improvements in behaviors incompatible with positive social engagement.

DSM-IV to DSM-5: Diagnostic and Treatment Implications

An important consideration is how treatment outcome research conducted with DSM-IV samples may or may not be generalizable to cases of DSM-5 ASD (see Box 3–1), which subsumes DSM-IV-TR autistic disorder, pervasive developmental disorder, and Asperger's disorder. In addition, DSM-5 includes a new diagnosis, social (pragmatic) communication disorder (SCD), that is separate from DSM-5 ASD and akin in certain cases to DSM-IV pervasive developmental disorder not otherwise specified (PDD-NOS), because routine and repetitive behaviors may not be present, as they now must be for criteria for DSM-5 ASD to be met. Cases of Asperger's disorder that do not involve broad enough impairment to meet DSM-5 ASD criteria will likely be "off the spectrum," or may be diagnosable as SCD if certain communication deficit criteria are met. Individuals with social deficits but no communication deficits or routine and repetitive behaviors will likely be excluded from a DSM-5 diagnosis of ASD or SCD, although these individuals' earlier history may have included communication and/or repetitive behaviors.

Clinically, the changes in DSM-5 present nosological difficulty, especially for teens and adults with higher-functioning autism or Asperger's disorder. From a research perspective, the transition from DSM-IV to DSM-5 will present a logistical nightmare for investigators in the middle of subject recruitment when the change occurs. National databases with data on individuals with DSM-IV autistic disorder and their families, such as those maintained by the Autism Genetic Resource Exchange and the Interactive Autism Network, will likely need to devise algorithms to map DSM-IV cases onto new criteria and caseness may be narrowed, resulting in exclusion of some already studied cases, possibly necessitating data re-analyses as sampling is completed.

Box 3–1. DSM-5 Diagnostic Criteria for Autism Spectrum Disorder

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A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behavior (see DSM-5, Table 2, p. 52).

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see DSM-5 text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behavior (see DSM-5, Table 2, p. 52).

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:

With or without accompanying intellectual impairment

With or without accompanying language impairment

Associated with a known medical or genetic condition or environmental factor

(**Coding note:** Use additional code to identify the associated medical or genetic condition.)
Associated with another neurodevelopmental, mental, or behavioral disorder (**Coding note:** Use additional code[s] to identify the associated neurodevelopmental, mental, or behavioral disorder[s].)
With catatonia (refer to the criteria for catatonia associated with another mental disorder, DSM-5, pp. 119–120, for definition) (**Coding note:** Use additional code 293.89 [F06.1] catatonia associated with autism spectrum disorder to indicate the presence of the comorbid catatonia.)

Twenty years ago, care was taken in transitioning from DSM-III-R (American Psychiatric Association 1987) to DSM-IV to capture the same cases, and for DSM-IV and the *International Statistical Classification of Diseases and Related Health Problems,* 10th Revision (ICD-10; World Health Organization 1992), to be concordant, although some expansion did occur. However, there is no analogous work to usher in DSM-5 ASD: SCD has no analog in ICD-10 and is not expected to have an analog in ICD-11. Therefore, it will be difficult to compare future samples based on DSM-5 diagnoses with samples based on ICD-10 or ICD-11 diagnoses of ASD, which may well contain SCD cases that were formerly diagnosed as DSM-IV PDD-NOS.

Practitioners, to whom this chapter is addressed, can expect diagnostic complications as well. For example, if a treatment is effective primarily in patients with DSM-IV Asperger's disorder but not in patients with DSM-IV autistic disorder, the mental health professional has to decide to which DSM-5 ASD cases results of such a study should be considered applicable (because Asperger's disorder and autistic disorder are no longer differentiated). If an individual from a DSM-IV study sample had been diagnosed with Asperger's disorder but lacked communication deficits, he or she may not be diagnosable with DSM-5 ASD or even with social communication disorder.

In addition, a group of early studies (e.g., McPartland et al. 2012) conducted in response to the proposed DSM-5 ASD diagnosis supports the idea that the new criteria may exclude some cases altogether. Those individuals no longer considered to be "on the spectrum," because they are no longer considered to have an ASD per DSM-5, may be excluded from treatments that had earlier been deemed empirically beneficial.

Another complicating issue is that individuals may now be classified as having both DSM-5 ASD and ADHD. Therefore, some individuals will now be included among ASD cases, although they previously were considered to have attention difficulty as the greater adaptive dysfunction and were diagnosed only with ADHD but not with autism disorder, despite meeting some of the criteria for DSM-IV autism disorder. The applicability of DSM-IV autism treatment outcome research may be questionable for such subjects, however, when attention deficit is a significant part of their clinical profile, and certainly their treatment needs and treatment responses may differ from those of subjects with only ASD.

In all practicality, until there is an accumulation of studies on the comparability of DSM-IV and DSM-5 samples and studies of treatment outcome research on subjects concurrently diagnosed using both classification systems, there will be a limited empirical basis for being certain that DSM-IV treatment outcome research applies across systems, especially for those patients previously diagnosed with DSM-IV Asperger's disorder or PDD-NOS and significant attention deficits presenting with secondary social deficits. Finally, the

utility of the DSM-5 ASD diagnosis can be questioned because it is neither mapped to biomarkers nor modeled on specific treatment-responsive traits as discussed here. For the near future, the interpreter of autism treatment outcome research needs to tread carefully, and attend carefully to indications about responder characteristics when moving from DSM-IV research on autistic disorder and pervasive developmental disorders to treatment of DSM-5 ASD.

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CHAPTER 4

Attention-Deficit/ Hyperactivity Disorder

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Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. According to data from the Centers for Disease Control and Prevention (2010), an estimated 5.4 million U.S. children ages 4–17 years have ADHD, representing a prevalence of 9.5%. ADHD is conceptualized as developmentally inappropriate levels of inattention, hyperactivity, and/or impulsivity (see Box 4–1 for DSM-5 [American Psychiatric Association 2013] diagnostic criteria). These core symptoms result in functional impairments in multiple settings, thus impacting family, academic, and social arenas.

The changes in criteria in the diagnosis of ADHD in DSM-5 from DSM-IV-TR (American Psychiatric Association 2000) are mostly related to making diagnosis easier in adults and include the following:

- *Fewer symptoms required for diagnosis in adults:* only five symptoms from either the inattentive domain or the hyperactivity/impulsivity domain are required (instead of six).
- *Age at onset:* DSM-5 raised the age criterion for presence of ADHD symptoms to 12 years (from age 7). This is important because it is always difficult for adults to remember early childhood.
- *Examples of adult symptoms:* Examples have been added of common adult ADHD symptoms to help in the diagnostic process.

In addition, for childhood ADHD:

- *Comorbidity with autistic spectrum disorder (ASD) allowed when criteria for both ADHD and ASD are met:* This change will allow more children to be diagnosed with ADHD, as previously autism excluded a diagnosis of ADHD.
- *ADHD placement under neurodevelopmental disorders rather than under diag-*

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noses usually originating in infancy, childhood, or adolescence: This change reflects the establishment of brain developmental correlates with ADHD.

Although ADHD is typically recognized and diagnosed when a child enters school, the condition is not restricted to school-age children. Significant symptoms may be present in younger children and often persist into adolescence and adulthood (Kessler et al. 2006). It is thought that 4%–5% of adults in the United States may have the disorder (Kessler et al. 2006). Community estimates of prevalence in preschool-age children range from 2% to 5% (Kollins et al. 2006).

Box 4–1. DSM-5 Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
   a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
   b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
   c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
   d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
   e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
   f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
   g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
   h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
   i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).
2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

a. Often fidgets with or taps hands or feet or squirms in seat.
b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
c. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
d. Often unable to play or engage in leisure activities quietly.
e. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
f. Often talks excessively.
g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

314.01 (F90.2) Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.

314.00 (F90.0) Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.

314.01 (F90.1) Predominantly hyperactive/impulsive presentation: If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Specify if:

In partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.

Moderate: Symptoms or functional impairment between "mild" and "severe" are present.

Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

ADHD is associated with a high psychosocial burden for both patients and their families and has a marked impact on normal functioning in home, school, and work settings (Biederman et al. 2006; Daley and Birchwood 2010; Wehmeier et al. 2010). ADHD can also have a significant financial toll on patients and their families in terms of the cost of medical care and work loss. According to Swensen et al. (2003), the annual average expenditure per patient with ADHD is almost three times the cost per matched control subject without ADHD. More recently, Pelham et al. (2007) reviewed the published literature and estimated the annual per-person cost of ADHD for children and adolescents to be almost $15,000 and estimated the annual cost of illness to U.S. society at $42.5 billion.

Undiagnosed or untreated ADHD is associated with significant morbidity and with consequences including counterproductive behavior, family problems including separation and divorce, diminished job performance, motor vehicle accidents and traffic violations, and secondary mood and anxiety disorders (Lamberg 2003). Research has shown that nontreated individuals with ADHD during childhood and adolescence have a greater risk of developing significant alcohol and substance abuse problems later in life than do individuals without ADHD (Wilens et al. 2003); however, when individuals have received treatment, the risk is reduced to that of non-ADHD individuals. Several other studies have also demonstrated that pharmacotherapy with stimulant medication has a significant protective effect by reducing the risk for later substance use disorders and cigarette smoking (Biederman and Faraone 2005; Wilens et al. 2008).

The management of ADHD symptoms consists of behavioral and pharmacological treatment administered separately or in combined, multimodal therapy. The practice parameter published by the American Academy of Child and Adolescent Psychiatry (AACAP; Pliszka and AACAP Work Group on Quality Issues 2007) provide evidence-based strategies for the diagnosis and treatment of ADHD.

The most recent published guideline of the American Academy of Pediatrics (2011) expands the group's 2001 recommendations (American Academy of Pediatrics 2001) to include preschool-age children. The new guideline addresses both diagnosis and treatment of ADHD in children ages 2 through 18 years. The strength of empirical evidence for a particular treatment is defined to range from rigorous randomized controlled trials, in which subjects have been randomly assigned to two or more treatment conditions, to uncontrolled or clinical opinion case reports.

Both academies' guidelines provide valuable input to scientists and clinicians on the treatment-related topics of evaluating and treating, comorbidities, preschoolers, and the management of treatment-emergent side effects. These topics are reviewed briefly in the following subsections.

Behavioral Treatment

A broad range of interventions are included under the rubric of behavioral, or nonmedical, therapy. They aim at altering the social and/or physical environment to modify children's behavior through parent behavior training, psychosocial therapy, and school-based programs.

Training helps parents learn to implement specific techniques based on behavioral principles when interacting with their child both at home and in other settings. Single families or groups of families attend weekly sessions in a clinical

practice over weeks or months. These services usually include homework sessions and give parents the opportunity to learn a variety of reward systems and strategies for providing consequences to shape behavior in multiple settings. In clinical practice, as well as in research studies, such training using a social learning approach typically includes 8–12 sessions, although the Multimodal Treatment Study of ADHD (MTA) was much lengthier, spanning 14 months (MTA Cooperative Group 1999). Parents typically learn such techniques as establishing daily report cards of target behaviors and implementing time-outs and reward systems (Table 4–1).

TABLE 4–1. Standard parent training sessions in a clinical behavioral intervention program

Session	Parent training topic
1	Overview: child's disorder, social learning theory, and behavior management principles
2	Establishing daily report cards for home and school and a home behavior checklist for rewarding home/school behavior
3	Attending to appropriate behavior and ignoring minor, inappropriate behavior
4	Giving effective reprimands and commands
5	"When…then contingencies"—establishing and enforcing rules
6	Using time-out procedures
7	Incorporating reward and response cost with a home point system
8	Enforcing contingencies and planning ahead for misbehavior outside of the home
9	Learning problem-solving techniques
10	Generalization—maintaining the program after therapist contact ends

Source. Adapted from Chronis et al. 2004.

Psychosocial therapy allows a trained therapist to speak with the child and family members in an individual or group setting about handling behaviors and emotions to improve social skills. Because of the Individuals With Disabilities Education Act of 2004 (IDEA; http://idea.ed.gov), special education services offered in public school settings must be designed to assist children with ADHD in their learning. Education specialists partner with teachers, parents, and children to create an individualized education program (IEP) to increase school success.

Limitations of behavioral treatment are similar to those of pharmacological treatment. The short-term effects of therapy usually are limited to the time period when the treatments are in effect; studies fail to show maintenance of these gains after the treatment ends. Also like pharmacological treatment, behavior therapy may result in large individual differences in response size. Some children do not show improvement, which

may be related to lack of parents' compliance in attending sessions and lack of follow-up with the school system. Research highlights the importance of including both parents and teachers in the delivery of such services (Pelham et al. 2000; Pfiffner et al. 2007).

Pharmacological Treatment

An estimated two-thirds of children ages 4–17 years with a current diagnosis of ADHD have received medication treatment for the condition (Centers for Disease Control and Prevention 2010). The primary treatment of ADHD is pharmacological, based on studies including that of the MTA Cooperative Group (1999), with an overwhelming consensus reporting benefits of multimodal treatment for comorbid symptoms. Use of pharmacological treatment is further supported by guidelines set forth by three major academies—the American Academy of Neurology, the American Academy of Child and Adolescent Psychiatry, and the American Academy of Pediatrics—as well as by international consensus (Kutcher et al. 2004). Although alternative treatments such as nutrition and exercise have been shown to improve psychiatric comorbidities, there is limited evidence to suggest their direct benefit for ADHD (Larzelere et al. 2010).

Stimulants are the most commonly prescribed pharmacological class of medication for ADHD. Methylphenidate, amphetamine, and pemoline (which is no longer available due to liver toxicity issues) make up this class of medications. Nonstimulant treatments, including atomoxetine, guanfacine, and clonidine, have been found to be beneficial both as monotherapies and adjuncts to stimulant therapy. Table 4–2 lists approved treatments for ADHD.

Pharmacological treatments for ADHD, with varied efficacy and duration of effects, continue to be developed and investigated to meet the specific needs of individual patients. Naturalistic clinic studies, as well as non-naturalistic randomized controlled trials (RCTs) that include clinic and laboratory school studies, are the prominent types of study designs that have influenced the investigation of ADHD drugs and the U.S. Food and Drug Administration's (FDA's) approval process for the pharmacological management of ADHD, are described in the next section.

Study Designs

Naturalistic and Non-Naturalistic Clinic Studies

A naturalistic setting is a relatively typical environment (home, school, workplace) in which individuals' behaviors are noted without researchers controlling the treatment assignment. For instance, observations of children with ADHD in school settings show that these children have difficulty sustaining attention on "boring" materials and blurt out answers, and may be forgetful in turning in homework assignments. Parents may report that at home, children with ADHD have difficulty staying seated at mealtime, talk excessively, and are disorganized. Naturalistic settings permit the study of effectiveness (how well the treatment works under typical use or in "real-world" situations). Thus, treatment strategies may seem more realistic by being less structured and more closely mimicking clinical practice implemented in routine medical care.

TABLE 4–2. U.S. Food and Drug Administration–approved medications used in the treatment of ADHD

Medication	Formulation	Mode of delivery	Metabolic, toxicological, and safety features
Stimulants			
Amphetamine	Dextroamphetamine sulphate	Immediate release	Common AEs: Insomnia, decreased appetite, weight loss, depression, anxiety, increased blood pressure/pulse Known to inhibit monoamine oxidase; minor inhibition of CYP2D6 Elimination influenced by urinary pH and flow rates
	Dextroamphetamine sulfate SR	Initial immediate release, remainder gradual release	
	Mixed amphetamine salts	Immediate release	
	Mixed amphetamine salts XR	50% immediate release (twice a day)	
Amphetamine prodrug	Lisdexamfetamine dimesylate	Activated in red blood cells when lysine is cleaved	
Methylphenidate	IR	Immediate release (chewable available)	Common AEs: Insomnia, decreased appetite, weight loss, depression, anxiety, increased blood pressure/pulse, skin irritation (with MTS) Less potent than amphetamine as CYP2D6 inhibitor
	SR	Gradual release	
	LA	50% immediate release (twice a day)	
	CD	30% immediate release 70% extended release	
	Osmotic-release oral system (OROS)	22% immediate release 78% gradual	
	Methylphenidate trans-	Patch worn up to 9 hours a day	

TABLE 4–2. U.S. Food and Drug Administration–approved medications used in the treatment of ADHD *(continued)*

Medication	Formulation	Mode of delivery	Metabolic, toxicological, and safety features
Methylphenidate *(continued)*	Quillivant XR	Extended-release liquid	
	Dexmethylphenidate	Immediate release	
	Dexmethylphenidate XR	50% immediate release (twice a day)	
Nonstimulants			
Noradrenergic agent	Atomoxetine	Immediate release	Common AEs: GI upset, nausea, sedation, insomnia, agitation; CYP2D6 inhibitors may increase atomoxetine steady-state plasma concentrations in EMs
α-Agonists	Clonidine	Extended release	Common AEs: Sedation, hypotension, bradycardia, constipation, dry mouth, increased appetite
	Guanfacine	Extended release	Common AEs: Similar to clonidine but less sedation; CYP3A4/5 inhibitors may increase rate and extent of guanfacine exposure

Note. AE=adverse effects; CD=controlled delivery; CYP=cytochrome P450; GI=gastrointestinal; IR=immediate release; LA=long acting; SR = sustained release; XR=extended release.
Source. Adapted from Duong et al. 2012.

Laboratory School Studies

A simulated laboratory classroom environment provides a non-naturalistic setting for measuring hour-by-hour effects of treatment. It also allows investigators to measure treatment outcomes in relation to serum concentrations among subjects. Both objective and subjective measures of behavior and cognition allow for the comparison of effects using active treatment versus placebo for ADHD symptoms (Wigal and Wigal 2006). Laboratory school staff is trained for consistency in conducting independent evaluations with precise timing of measurements in relation to dosing of medication. These studies, utilizing RCT, inform about "efficacy," or how well the treatment works, as well as dosing, delivery, and safety profile information, in an optimized laboratory setting with fixed treatment or treatment groups. Initial research with this type of model conducted at sites across the country studied novel stimulant or nonstimulant dosing, delivery, and safety using capsule or tablet oral medication formulations.

Laboratory school studies have led to the development of osmotic-release oral system (OROS) methylphenidate hydrochloride extended-release tablets (Concerta) (Swanson et al. 1998b, 1999a, 2002, 2003, Wigal et al. 1998, 2011a), extended-release mixed amphetamine salts (MAS XR, Adderall XR) (ADDERALL XR Medication Guide 2011; Greenhill et al. 2003; McCracken et al. 2003), Metadate CD (Swanson et al. 2004; Wigal et al. 2003), and Focalin (Quinn et al. 2004). Also, transdermal, liquid, and chewable delivery systems have been studied with the laboratory school protocol. In addition, the development of procedures and methodology has allowed such analog classroom studies to be conducted across the lifespan, from preschool through high school and in adulthood. Such studies also have been designed and conducted for additional indications and areas of interest. For instance, a comprehensive postmarketing study of Concerta assessed treatment effects on the academic, behavioral, and cognitive difficulties experienced by older children with ADHD (Wigal et al. 2011b). In addition to incorporating the typical laboratory school measures such as parent and teacher ratings, trained observer ratings of attention and deportment, and effort on grade-level math tests, standardized measures of reading proficiency (fluency and comprehension) and handwriting, as well as grammar tasks and other homework-like tasks, were also studied. Thus, the laboratory school design has contributed to the clinical understanding of medicines for the treatment of ADHD for specific symptoms as well as broader clinical and cognitive impairments.

Stimulant Treatment

The use of stimulants to treat ADHD is very efficacious. The effect size of a treatment in the context of a clinical trial is a statistical calculation showing the strength of a particular treatment compared with placebo or an alternative comparable treatment. An effect size of 0.5 is considered large, an effect size of 0.3 is considered medium, and an effect size of 0.1 is considered small. When effect size is calculated for stimulant treatment of ADHD using various outcome measures of clinical response, such as behavioral rating scales of attention and focus, the effect size is very large, typically 1.0 or greater.

Since 2000, various longer-acting medications have been studied and approved for treating ADHD. Their advantages over immediate-release forms include a

smaller number of doses required per day to control ADHD symptoms throughout the day; greater patient privacy about diagnosis and treatment in school, work, and extracurricular settings; greater convenience; and the potential for greater adherence to treatment.

Methylphenidate Formulations

Methylphenidate was the first stimulant approved by the FDA for treating ADHD and remains a standard therapy in current treatment guidelines. Methylphenidate was available initially as an immediate-release (IR) dosage formulation, and later as sustained-release (SR), long-acting (LA), controlled-delivery (CD), and extended-release (XR) formulations, as well as OROS (Figure 4–1) and the methylphenidate transdermal system (MTS), which provide various durations of effects. Chewable and liquid forms are also available. Newer longer-acting methylphenidate formulations have combined immediate-release and extended-release or sustained-release technologies (Wigal et al. 2006b) and have been studied using the laboratory school protocol as a tool to measure product efficacy, onset, and duration.

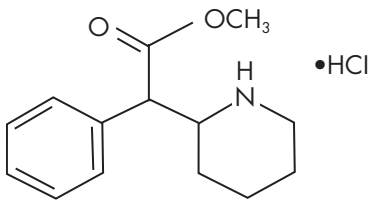

FIGURE 4–1. Concerta.
Mechanism of action/pharmacology: Methylphenidate HCl stimulant; blocks reuptake of norepinephrine and dopamine in the presynaptic neuron to increase their availability into the extraneuronal space. *Route of administration:* Oral (once daily). *Chemical structure:* methyl α-phenyl-2-piperidineacetate hydrochloride.
Source. Prescribing information, http://www.concerta.net/adult/prescribing-information.html.

The therapeutic activity of methylphenidate resides in the D-isomer of the racemic *threo*-methylphenidate. Most methylphenidate preparations are a racemic mixture of the D- and L-*threo* enantiomers of methylphenidate; however, two dexmethylphenidate (methyl α-phenyl-2-piperidineacetate hydrochloride) products (Focalin and Focalin XR) are composed of only the D-*threo* enantiomer.

A novel extended-release liquid formulation of methylphenidate, NWP06 (Quillivant; Figure 4–2), has been approved by the FDA for treating ADHD in patients ages 6–65 years. This formulation was designed to avoid the medication compliance challenges of solid extended-release dosage forms. One laboratory school study (Wigal et al. 2013) conducted at two sites demonstrated both onset (45 minutes) and duration (12 hours) of NWP06 in children ages 6–12 years. NWP06 was safe and well tolerated during the study, and adverse events were consistent with known effects of methylphenidate and not clinically significant.

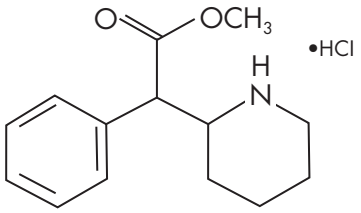

FIGURE 4–2. Quillivant XR.
Mechanism of action/pharmacology: Methylphenidate HCl stimulant; blocks reuptake of norepinephrine and dopamine in the presynaptic neuron to increase their availability into the extraneuronal space. *Route of administration:* Oral (once daily with or without food). *Chemical structure:* methyl α-phenyl-2-piperidineacetate hydrochloride.
Source. Prescribing information, http://labeling.pfizer.com/ShowLabeling.aspx?id=965.

Amphetamine Formulations

Amphetamine-based compounds used to treat ADHD include dextroamphetamine sulfate and short-acting and extended-release mixed amphetamine salts (MAS). MAS combines the sulfate salts of D-amphetamine (75%) and L-amphetamine (25%) with the D-isomer of amphetamine saccharate and D,L-amphetamine aspartate monohydrate. Lisdexamfetamine dimesylate is classified as an amphetamine but in the subcategory of prodrug.

Lisdexamfetamine dimesylate (LDX; Vyvanse) (Figure 4–3), approved for treating children, adolescents, and adults with ADHD, is the first prodrug stimulant approved by the FDA for the management of ADHD symptoms (U.S. Food and Drug Administration 2007). A *prodrug* is defined as "any compound that undergoes biotransformation before exhibiting its pharmacological effects" (Stanczak and Ferra 2006). Clopidogrel (Plavix) is an example of a prodrug used to treat patients with cardiovascular disease to reduce the risk of heart attack and other cardiac issues by decreasing the likelihood of blood clotting. LDX is hydrolyzed by endogenous enzymes in the blood by red blood cells to L-lysine, a naturally occurring essential amino acid, and the single enantiomer D-amphetamine, the source of its therapeutic action (Pennick 2010). LDX is approved in the United States in dosage strengths of 20, 30, 40, 50, 60, and 70 mg for children age 6 years and older, adolescents, and adults. Less inter- and intrapatient pharmacokinetic variability is reported with LDX, with reduced interindividual differences in gastric acidity and gastrointestinal transit times as compared with beaded formulations (Krishnan and Zhang 2008; Shire 2011).

Several clinical studies of LDX in both a laboratory school setting and a more naturalistic setting have been completed with children ages 6–12 years who have ADHD. In a 6-week, randomized, double-blind, crossover study, LDX was effective in reducing ADHD symptoms compared with placebo ($P<0.0001$), according to SKAMP (Swanson, Kotkin, Agler, M-Flynn, and Pelham) scale deportment scores. Efficacy was demonstrated from 2 hours postdose, the first time point measured, until 12 hours postdose, the last time point measured (Biederman et al. 2007a). This study was followed by a 4-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial with LDX (30, 50, and 70 mg/day) over 4 weeks of treatment to

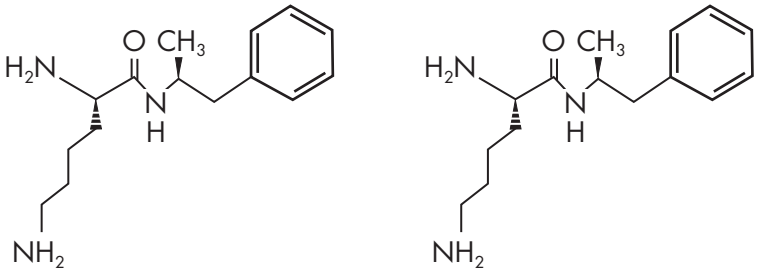

FIGURE 4–3. Vyvanse.
Mechanism of action/pharmacology: Prodrug; conversion to L-lysine and active D-amphetamine after ingestion/blocks reuptake of norepinephrine and dopamine in the presynaptic neuron to increase their availability into the extraneuronal space. *Route of administration:* Oral. *Chemical structure:* (2S)-2,6-diamino-*N*-[(1S)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate. *Source.* Prescribing information, http://pi.shirecontent.com/PI/PDFs/Vyvanse_USA_ENG.pdf

evaluate LDX safety and efficacy (Biederman et al. 2007b). Compared with placebo, all doses showed significant improvements ($P<0.001$) in ADHD Rating Scale Version IV (ADHD-RS-IV) scores beginning with the first week of LDX treatment. Likewise, parent ratings on the ADHD Index of the Conners' Parent Rating Scale (CPRS) showed significant improvement for LDX compared with placebo ($P<0.001$) at each of the time points measured, at about 10 A.M., 2 P.M., and 6 P.M. ($P<0.001$). LDX was generally well tolerated in terms of safety. The following laboratory school study included a larger sample size (129 vs. 52) and additional time points assessed, at predose and 13 hours postdose, expanding on the previous work (Wigal et al. 2009).

Nonstimulant Formulations

Although stimulant treatments have been considered the "gold standard" for treating ADHD, about 70% of patients respond to the introduction of a first stimulant, and the response rate increases to 90% in nonresponders switched to a second stimulant (Elia et al. 1991). Nonstimulants, another treatment option, have also been shown to be effective in treating patients with ADHD. Nonstimulants may be the only feasible option for those 10%–30% of patients with ADHD who do not respond to stimulant therapy or who experience adverse reactions with or must avoid this class of medications (Mohammadi and Akhondzadeh 2007). Nonstimulants, however, seem to have much smaller clinical effects than stimulants. Nonstimulants approved by the FDA for the treatment of ADHD include atomoxetine, a long-acting form of guanfacine, and a long-acting form of clonidine (see Table 4–2). Each of these medicines is considered unscheduled; therefore, they are not controlled substances and have no known potential for abuse or dependence. Guanfacine and clonidine also have been approved for coadministration with stimulant treatment.

Selective Norepinephrine Reuptake Inhibitors

Atomoxetine (Strattera), a selective norepinephrine reuptake inhibitor, was the first nonstimulant approved for ADHD in the United States (Figure 4–4). Atomoxetine is thought to increase concentrations of norepinephrine and dopamine by acting on the presynaptic norepineph-

rine transporter in the prefrontal cortex (Banaschewski et al. 2004; Mohammadi and Akhondzadeh 2007). Norepinephrine and dopamine in other brain regions, including the striatum and nucleus accumbens, are also impacted by atomoxetine and may underlie its low abuse potential.

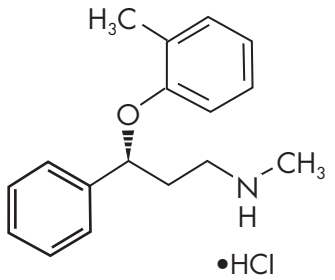

FIGURE 4–4. Strattera.
Mechanism of action/Pharmacology: Blocks reuptake of norepinephrine in the presynaptic neuron to increase its availability into the extraneuronal space. *Route of administration:* Oral. *Chemical structure:* (-)-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)-propylamine hydrochloride.
Source. Prescribing information, http://pi.lilly.com/us/strattera-pi.pdf.

α_2-Adrenergic Agonists

Immediate-release clonidine and guanfacine, both α_2-adrenergic agonists, have been used for years in the treatment of ADHD, yet only the extended-release forms of these nonstimulants have FDA approval for ADHD. Recent evidence suggests that extended-release clonidine (clonidine XR) provides added efficacy when treating ADHD in youths ages 6–17 years who have had inadequate response to stimulants (Kollins et al. 2011). Clonidine XR (Kapvay; Figure 4–5) is the first FDA-approved α_2 add-on agent for use with stimulants to treat ADHD. The common side effects are low blood pressure and low heart rate and sleepiness. Gradual dose reductions for terminating treatment are recommended to minimize withdrawal symptoms such as rebound hypertension and lightheadedness.

Extended-release guanfacine (Intuniv) is the first α_2-adrenergic agonist for treating ADHD. Sedation is a common side effect of guanfacine, although it is thought to diminish over time (Faraone and Glatt 2010). Guanfacine should not be taken with high-fat meals, which can markedly increase its exposure compared with administration during a fasted state (e.g., C_{max} may increase by 75%; Intuniv Prescribing Information 2011).

Use of "Rational Polypharmacy"

Although there is a growing trend toward the combined use of FDA-approved medications, it is questionable whether employing such polypharmacy for the treatment of ADHD would be helpful or harmful. The understood goal of polypharmacy is "to produce a drug-drug interaction that will have beneficial consequences for the patient" (Preskorn and Lacey 2007, p. 98). For such polypharmacy to be considered rational, research must demonstrate the value of isolated versus combined treatments in terms of

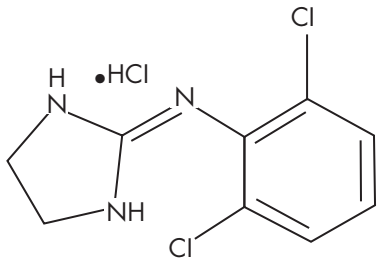

FIGURE 4–5. Kapvay.
Mechanism of action/pharmacology: Stimulates α_2-adrenergic receptors/reduces sympathetic outflow, decreases peripheral and renal vascular resistance, and heart rate. *Route of administration:* Oral. *Chemical structure:* 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride.
Source. Prescribing information, http://www.kapvay.com/pdf/Kapvay-PI.pdf.

safety and efficacy (Niculescu and Hulvershorn 2010). At the present time, only two medications—GXR and CLON-XR—have sufficient evidence to support FDA approval for adjunctive therapy with stimulant medications (American Academy of Pediatrics 2011); Kollins et al. 2011; Sallee et al. 2012). Other medications used in combination off-label treatment have only anecdotal support of safety and/or efficacy; therefore, their use cannot be recommended. Currently, monodrug therapy still is viewed as the ideal.

Comorbid Disorders

Other psychiatric disorders may co-occur with ADHD. Patients may present with symptoms that are in addition to those of ADHD, in which case they would qualify as a separate disorder, or are secondary to the primary ADHD diagnosis. In the former case, the disorder with the greatest impairment is typically the one influencing the treatment regimen. Also of note is that because there is a high heritability of ADHD, management of ADHD symptoms in affected parents is actually an important part of each child's treatment.

Treatment-Emergent Side Effects

Typically, two formats are favored for the collection of adverse event reports: 1) general inquiry with open-ended questions and 2) spontaneous reporting by child and/or parent. A third method, structured interview with specific queries, is thought to bias the collection of adverse event reports and therefore is seldom used in clinical trials and clinical visits. Physicians generally record the duration of adverse events, severity (mild, moderate, severe, and serious), and relation to study drug.

Commonly observed adverse effects may include appetite suppression, headache, insomnia, irritability, and abdominal pain. Short-term reductions in expected height and weight due to stimulant therapy have been shown, but the question of the long-term impact of psychostimulants on growth still needs to be addressed in targeted, large-scale studies. Biannual monitoring of height, weight, and body mass index for surveillance of significant changes helps clinicians in considering drug holidays or dose alterations (Pliszka and AACAP Work Group on Quality Issues 2007).

Sudden cardiac death and concern about structural cardiac abnormalities and cardiovascular effects from pharmacotherapy have been written about extensively, as has the debate over obtaining an electrocardiogram (ECG) prior to initiating treatment with stimulants or norepinephrine reuptake inhibitors. A thorough family history of cardiac events (arrhythmia, sudden unexpected death, hypertrophic cardiomyopathy, Marfan syndrome) and personal cardiac history (palpitations, syncope, chest pain, prior surgeries, congenital heart conditions, murmur, arrhythmia) with regular blood pressure and auscultation examinations are an important part of the ADHD evaluation (Steinberg-Epstein et al. 2011). Positive findings or concerns based on cardiac history or physical examination necessitate further evaluation with ECG, echocardiogram, and/or cardiology referral (Perrin et al. 2008). Childhood use of psychostimulants may be associated with increased heart rate several years following discontinuation (Vitiello et al. 2012).

Thus, risk-benefit analyses assist in the management of side effects. The goal of titrating a medication to a patient's clinically best dose is to achieve optimal efficacy with minimal side effects. The use of dose titration in clinical trials closely simulates the medication management conducted in clinical settings. In the naturalistic clinic setting, one role of prescribers is to educate patients and their family to recognize this balance so they can make informed decisions about whether increasing medication doses or switching medications is the preferred option for further treatment benefits. Clearly, the decision to treat ADHD should not be taken lightly, yet the negative impact of both primary (hyperactivity, impulsivity, and inattention) and secondary (agitation, anxiety, and depression) features of ADHD on quality of daily life is evident.

Preschool-Age Children

ADHD has expanded from being seen as solely a childhood disorder in elementary school–age children to being viewed as a disorder across the lifespan, which includes preschoolers. The Preschool ADHD Treatment Study (PATS; Kollins et al. 2006), a six-site study funded by the National Institute of Mental Health (NIMH), recognized the startling increase in stimulant prescriptions written for preschoolers, as well as the lack of diagnostic and treatment consensus for these children. Because the lowest age approved for use of methylphenidate by FDA guidelines is 6 years, one of the primary aims of the study was to investigate the drug's safety and efficacy in children ages 3–5.5 years (at screening) (Greenhill et al. 2006). Stimulant dosing generally does not follow by-weight guidelines; therefore, younger and smaller children may receive relatively higher by-weight doses than older and larger children, and they may be more prone to risk for dose-dependent adverse events (Wigal et al. 2006a). Although multiple publications have emerged from the PATS, a pharmacokinetic add-on study highlighted here (Table 4–3) demonstrated slower clearance in preschoolers than in school-age children with ADHD. Thus, even when the variable of weight is controlled for, allowing for a different volume of distribution from older children, preschoolers respond differently to stimulants than do school-age children (Wigal et al. 2007).

Conclusion

Significant advances in the treatment of ADHD have occurred since 2000, with improved formulations and drug delivery systems. The broad range of pharmacological treatments available allows for

TABLE 4–3. Pharmacokinetic parameters: comparison of methylphenidate in preschool- and school-age subjects

	Preschool-age children	School-age children	Difference in effect size	*P*
Age	5.33±0.56	8.00±0.56	4.77	<0.001
Weight (kg)	19.2±2.6	28.3±5.8	2.22	<0.001
Dose (mg)	5.89±1.9	6.94±3.3	0.42	0.33
Dose/weight (mg/kg)	0.311±0.09	0.252±0.13	−0.54	0.20
CL/F (L/hour)	99.5±44	232.6±75	2.52	<0.001
CL/F/weight (L/hour/kg)	5.12±1.9	7.91±1.6	1.52	0.01
Half-life (hours)	3.82±2.7	2.18±0.3	−0.69	0.46
C_{max} (ng/mL)	10.2±5.0	7.6±4.2	−0.53	0.32
1,000*C_{max}/D (1/L)	1.72±0.5	1.10±0.3	−1.44	0.003

Note. CL=total body clearance; CL/F=oral clearance; C_{max}=peak plasma concentration; C_{max}/D=peak plasma concentration by dose.
Source. Adapted from Wigal et al. 2007.

both single and combination therapies for achieving optimal therapeutic effects. Yet, one of the key issues facing researchers investigating these treatments involves establishing a target for ADHD symptom improvement that will generalize to alleviation of impairment that is meaningful to patients and their families. Achieving a 25%–30% improvement in symptom severity on parent-, clinician-, or teacher-rated symptom checklists is generally considered a positive response; however, this level of symptom reduction may still leave individual children with clinically significant impairment. A recent proposal suggested that optimal treatment (remission) is achieved by lowering ADHD symptom scores to within the range of those of typically developing children (Steele et al. 2006). The determination of the goals of medication titration in an individualized manner is important for clinical interpretation of treatment effects. Practitioners now have the opportunity to use an evidence basis for customizing ADHD treatment in pediatric patients with an appropriate risk-benefit ratio.

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CHAPTER 5

Specific Learning Disorder

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According to DSM-5 (American Psychiatric Association 2013), specific learning disorder (LD) comprises a heterogeneous group of disorders characterized by persistent difficulties with learning academic skills in a variety of domains, including reading, spelling, written expression, and mathematics (Box 5–1). The symptoms of specific LD must have persisted for at least 6 months, even though interventions that target those difficulties were provided. Furthermore, the affected academic skills must be substantially and quantifiably below levels expected for the person's age and cause interference with academic or occupational performance or with activities of daily living (based on a clinical synthesis of the individual's history, school reports, and psychoeducational assessment). The learning difficulties are not accounted for by intellectual disabilities, by uncorrected problems with visual or auditory acuity, or by lack of language proficiency, inadequate educational instruction, or psychosocial adversity. The academic domains and subskills that are impaired are specified within each of the following domains: reading (word reading accuracy, reading rate or fluency, reading comprehension), written expression (spelling accuracy, grammar and punctuation accuracy, clarity or organization of written expression), and mathematics (number sense, memorization of arithmetic facts, calculation fluency or accuracy, accurate math reasoning). Finally, the severity of the LD is identified.

Although comorbidity across types of LD is notably high, treatments typically target the particular features of each specific type of LD. Nevertheless, a literature review indicates that there are guiding principles for treatment that apply to all areas of LD. In this chapter, we begin with a discussion of these general guidelines, then describe treatments for the different kinds of impairment in LD, and finally discuss the implications of disorders often comorbid with LD. Although most academic interventions take place within the school system or through programming

available through specialists, this chapter focuses on what has been shown to work and what characteristics specific to LD can be effectively targeted for intervention.

Box 5–1. DSM-5 Diagnostic Criteria for Specific Learning Disorder

A. Difficulties learning and using academic skills, as indicated by the presence of at least one of the following symptoms that have persisted for at least 6 months, despite the provision of interventions that target those difficulties:
   1. Inaccurate or slow and effortful word reading (e.g., reads single words aloud incorrectly or slowly and hesitantly, frequently guesses words, has difficulty sounding out words).
   2. Difficulty understanding the meaning of what is read (e.g., may read text accurately but not understand the sequence, relationships, inferences, or deeper meanings of what is read).
   3. Difficulties with spelling (e.g., may add, omit, or substitute vowels or consonants).
   4. Difficulties with written expression (e.g., makes multiple grammatical or punctuation errors within sentences; employs poor paragraph organization; written expression of ideas lacks clarity).
   5. Difficulties mastering number sense, number facts, or calculation (e.g., has poor understanding of numbers, their magnitude, and relationships; counts on fingers to add single-digit numbers instead of recalling the math fact as peers do; gets lost in the midst of arithmetic computation and may switch procedures).
   6. Difficulties with mathematical reasoning (e.g., has severe difficulty applying mathematical concepts, facts, or procedures to solve quantitative problems).

B. The affected academic skills are substantially and quantifiably below those expected for the individual's chronological age, and cause significant interference with academic or occupational performance, or with activities of daily living, as confirmed by individually administered standardized achievement measures and comprehensive clinical assessment. For individuals age 17 years and older, a documented history of impairing learning difficulties may be substituted for the standardized assessment.

C. The learning difficulties begin during school-age years but may not become fully manifest until the demands for those affected academic skills exceed the individual's limited capacities (e.g., as in timed tests, reading or writing lengthy complex reports for a tight deadline, excessively heavy academic loads).

D. The learning difficulties are not better accounted for by intellectual disabilities, uncorrected visual or auditory acuity, other mental or neurological disorders, psychosocial adversity, lack of proficiency in the language of academic instruction, or inadequate educational instruction.

Note: The four diagnostic criteria are to be met based on a clinical synthesis of the individual's history (developmental, medical, family, educational), school reports, and psychoeducational assessment.

Coding note: Specify all academic domains and subskills that are impaired. When more than one domain is impaired, each one should be coded individually according to the following specifiers.

Specify if:

315.00 (F81.0) With impairment in reading:

Word reading accuracy
Reading rate or fluency
Reading comprehension

Note: *Dyslexia* is an alternative term used to refer to a pattern of learning difficulties characterized by problems with accurate or fluent word recognition, poor decoding, and poor spelling abilities. If dyslexia is used to specify this particular pattern of difficulties, it is important also to specify any additional difficulties that are present, such as difficulties with reading comprehension or math reasoning.

315.2 (F81.81) With impairment in written expression:

Spelling accuracy

Grammar and punctuation accuracy

Clarity or organization of written expression

315.1 (F81.2) With impairment in mathematics:

Number sense

Memorization of arithmetic facts

Accurate or fluent calculation

Accurate math reasoning

Note: *Dyscalculia* is an alternative term used to refer to a pattern of difficulties characterized by problems processing numerical information, learning arithmetic facts, and performing accurate or fluent calculations. If dyscalculia is used to specify this particular pattern of mathematic difficulties, it is important also to specify any additional difficulties that are present, such as difficulties with math reasoning or word reasoning accuracy.

Specify current severity:

Mild: Some difficulties learning skills in one or two academic domains, but of mild enough severity that the individual may be able to compensate or function well when provided with appropriate accommodations or support services, especially during the school years.

Moderate: Marked difficulties learning skills in one or more academic domains, so that the individual is unlikely to become proficient without some intervals of intensive and specialized teaching during the school years. Some accommodations or supportive services at least part of the day at school, in the workplace, or at home may be needed to complete activities accurately and efficiently.

Severe: Severe difficulties learning skills, affecting several academic domains, so that the individual is unlikely to learn those skills without ongoing intensive individualized and specialized teaching for most of the school years. Even with an array of appropriate accommodations or services at home, at school, or in the workplace, the individual may not be able to complete all activities efficiently.

General Treatment Guidelines

Facilitate Intervention and Identification as Early as Possible

The importance of early intervention cannot be overstated because the earlier the intervention, the better the outcome (Perez-Johnson and Maynard 2007; Strickland 2002). Given the persistent nature of LD and the increased likelihood of complicating factors when LD is left untreated, later intervention will be more intensive and costly as well as less effective (Steele 2004). Early intervention that is directed more toward prevention than treatment and that helps families obtain access to educational programs and clinical services before the child is allowed to fail for several grades is of particular value. The most common early risks are delayed

language development and specific language features including mispronouncing words, word-finding problems, trouble rhyming, and difficulty learning the alphabet (Catts 1997; Shaywitz 2003).

Refer for Individualized Assessment

Referral for individualized assessment is especially important for older children or those who have not responded to early intervention. The assessment should include standardized and well-validated tests to determine a child's level of functioning and relative strengths and weaknesses in both cognitive and academic domains. Reliance on a discrepancy between IQ and achievement as the sole requirement for diagnosing LD, however, is not advised given ample evidence that this discrepancy is not particularly informative, is psychometrically problematic, and is typically unrelated to intervention outcomes (Fletcher et al. 2005). In keeping with the guidelines in DSM-5, designation of LD should rely on a compilation of assessment results, school performance, and individual history.

Opt for Evidence-Based Treatments

There is a growing understanding that evidence-based interventions are of maximal benefit both for helping the individual child and for moving the field of treatment research forward. The U.S. federal No Child Left Behind Act of 2001 (P.L. 107-110) calls on practitioners to use scientifically based research in their decision-making and intervention practices. The best research design for evaluating an intervention's effectiveness is a randomized controlled trial, and treatments that stand up to this test should be recommended over those that do not. Although specific recommendations are included in the discussion of LD subtypes in the next section of this chapter, general guidelines on how best to determine if an intervention is evidence based may be helpful to both clinicians and families advocating on behalf of a child. This information is available in peer-reviewed journals and academic books, as well as through the What Works Clearinghouse, which hosts a Web-based informational site created by the Institute of Educational Sciences of the U.S. Department of Education (http://ies.ed.gov/ncee/wwc).

Track Response to Treatment Over Time and Design Treatments to Target Particular Aspects of Development Within an Academic Domain

Gains resulting from a specific intervention may be differentially maintained over time, and academic demands change as a child progresses. Thus, a specific intervention may be helpful for a particular child at one age but may not address issues that arise at a later age. For example, although the core deficit of reading disorder is typically difficulty with recognizing and manipulating the individual sounds in words (phonological awareness), intervention should go beyond this specific skill and include other aspects of reading, such as fluency and comprehension, as the reader progresses. Furthermore, given that there is no "one-size-fits-all" treatment for LD, tracking an individual child's response to treatment and his or her progress across academic and developmental domains is essential.

Treatments for Learning Disorder by Specific Impairments

Impairment in Reading (Reading Disorder)

Reading disorder or disability (RD), classified in DSM-5 as specific LD with impairment in reading, occurs in isolation or in combination with another LD in 70%–80% of children with LD (Lyon et al. 2003). Reading difficulties can be encountered at several levels, including problems with recognizing and decoding single words, comprehending continuous text, or reading rate and fluency. The widespread consensus among reading researchers is that the core deficit for RD is difficulty with phonological awareness—the ability to recognize and manipulate individual sounds in words (Melby-Lervåg et al. 2012). Awareness of individual sounds in words is important for learning to associate sounds to the letters that represent them in print. Thus, phonological awareness is a necessary, though not sufficient, first step to reading acquisition. Given its importance, phonological awareness is the focus of many interventions for RD. This work is often coupled with phonics training in which children are taught 1) the correspondence between letters and sounds when "sounding out" unfamiliar words and 2) spelling patterns typically used to represent these sounds. In a review and meta-analysis of research studies on reading interventions and instructional approaches, the National Reading Panel concluded that phonemic awareness instruction produced improvements in reading development in both young normally achieving children and older children with RD (Ehri et al. 2001; National Reading Panel 2000). Furthermore, the group reported that the most effective instruction was direct, explicit, and systematic (rather than unstructured), was focused on a limited set of phonemes at one time, and took place in small groups or with one-to-one instruction. They went on to warn, however, that phonemic awareness training should constitute a part and not the whole focus for reading intervention.

Other aspects of reading, including instruction in letter-sound correspondences, reading fluency, and comprehension, are also required. The National Reading Panel (2000) noted that systematic phonics instruction (i.e., instruction involving tightly controlled and sequentially organized instructional materials) was superior to more incidental approaches in which phonics are highlighted as they are encountered in text. Systematic phonics instruction was shown to have benefits for students across a range of grades, abilities, and income levels. Phonics instruction was clearly identified as a means to an end, however, in that it is a tool for helping children learn to decode text. As with phonological awareness training, phonics instruction needs to be applied to reading and spelling and should not be the sole focus for intervention. These findings provide clear support for the importance of providing structured and focused instruction in phonics and phonemic awareness as part of the treatment for children with RD. In addition to school-based programs, many commercial treatment programs are available that target phonological processing skills.

Instructional strategies for reading skills beyond single-word decoding, such as reading comprehension, have also been identified (e.g., Duff and Clarke 2011). Studies of children with RD who have adequate single-word reading

skills but are impaired in comprehension indicate that this subgroup of children have problems in oral language skills, including problems with expressive and receptive language, listening comprehension, and grammatical understanding (Nation et al. 2010). In a review of reading comprehension interventions over the last 30 years, Solis et al. (2012) reported that the majority of studies showing large effect sizes used summarization or main idea instruction strategies. A comprehensive assessment that includes oral language functioning as well as assessment of reading skills beyond reading of single words is recommended for all children with RD.

The rate or fluency with which children read has implications for reading comprehension. Children with RD are also exposed to less text than their average reading peers, in part because their reading difficulties reduce the likelihood that they will read for pleasure or be able to master longer, more challenging texts. Thus, intervening to improve reading rate can have numerous benefits. Several meta-analyses have demonstrated that a method of practice known as repeated reading improves both reading fluency and comprehension (Chard et al. 2002; National Reading Panel 2000; Therrien 2004). It should be noted, however, that a recently published systematic review using strict criteria for the quality of studies included in the review yielded less compelling evidence than previous meta-analyses (O'Keeffe et al. 2012). Despite this proviso, some discussion of the repeated reading technique is warranted because this technique can be easily adapted for use both in the home and in school. It involves having the child repeatedly read a passage of text aloud until he or she is able to do so fluently and accurately; assisted repeated reading has been shown to enhance fluency when the child is reading along with an adult, skilled peer, or audio recording of the text (Shany and Biemiller 1995; Young et al. 1996).

Taken together, the research to date clearly indicates that most efficacious treatments for RD are *structured, targeted* interventions addressing core deficits in the areas of phonological awareness and phonemic decoding skills, comprehension skills, and reading fluency. It is important to note, however, that not all children will respond to these interventions (Torgesen 2000). In fact, lack of response to intervention has been proposed by some as an alternative to the widely used, although much criticized, discrepancy between IQ and achievement for identifying a child as having an RD (e.g., Speece and Case 2001). More research is required, however, to clarify how best to treat children with treatment-resistant characteristics. Increasing the intensity or frequency of established interventions may be helpful, although this is yet to be demonstrated. The impact of learner characteristics on treatment responsiveness underscores the need for thorough assessment and follow-up of children even after they have received treatment.

Impairment in Written Expression (Written Expression Learning Disorder)

Given the complex nature of writing, the characteristics of written expression learning disorder (WLD) also vary widely. Problems with motor control, for example, make the mechanics of writing difficult, whereas language-based difficulties can negatively impact the representation

of letters and words in text, spelling, grammar, and punctuation (Berninger and Amtmann 2003). All of these difficulties affect the speed or fluency with which an individual with WLD can perform writing activities. Finally, higher-level skills, such as planning, generating and organizing ideas into text, and reviewing and editing, have all been shown to be particularly problematic for individuals with WLD (Graham and Harris 2003). Although there is a high degree of overlap between RD and WLD, these disorders do not always co-occur, and WLD can be a unique area of difficulty for some individuals (James and Selz 1997). Recently, Berninger and May (2011) put forward three specific WLDs based on characteristic phenotypes arising from the research literature: dysgraphia (impaired automatic letter writing, orthographic coding, and finger sequencing), dyslexia (impaired pseudo-word reading, spelling, phonological and orthographic coding, and certain executive functions), and oral and written language LD (e.g., dyslexia plus morphological and syntactic coding and comprehension problems).

Treatments for WLD, according to Berninger and May (2011), should target the constellation of strengths and weaknesses associated with the specific types of WLD outlined above. Treatments for WLD can be roughly divided into two main areas: those that focus on transcription (i.e., the production of letters and spelling) and those that focus on composition skills (e.g., idea generation, organization, and editing). These interventions are far from independent, however, because improvements in lower-level skills, such as handwriting speed and accuracy, can free up resources for other writing components, such as planning and reviewing (Berninger and Amtmann 2003). Educational and remedial interventions for transcription problems include direct modeling of letter formation followed by extensive practice to enhance automaticity. Effective handwriting training has also been shown to improve composition fluency and quality (Berninger et al. 1997). Spelling interventions typically include a combination of training in phonological awareness, phoneme-spelling correspondences, and direct instruction in spelling convention rules (for a review, see Berninger and Amtmann 2003).

A recent meta-analysis that examined writing instruction for elementary school students (Graham et al. 2012) identified several writing interventions that produce statistically significant effects. The programs varied widely and included interventions that explicitly teach writing process skills as well as programs that include procedures for scaffolding or supporting student writing. Word processing, extra writing, and comprehensive writing programs were also shown to be effective. In another meta-analysis, Graham and Harris (2003) demonstrated that an instructional technique called Self-Regulated Strategy Development (SRSD), involving explicitly teaching the same strategies for writing used by skilled writers, substantially improves the quality of writing produced by individuals with WLD. Key components of SRSD include direct instruction in identifying and using effective writing strategies and enhancement of self-regulation by modeling and instructing students to memorize and repeatedly apply strategies so that they can use them independently in their writing.

Finally, when writing problems persist even with intervention, accommodations, such as extra time allowances on tests and written assignments, and access to computers for word processing,

are important for the academic and vocational success of individuals with WLD. It is important to note, however, as was pointed out by Berninger and Amtmann (2003), that computer technology may not be a "quick fix" for writing problems. Issues to consider include the individual's needs and abilities, the likelihood that computer technology will be feasible in addressing these needs, the time and resources needed to make use of the technology, and the environment in which the tool will need to be used.

Impairment in Mathematics (Mathematics Learning Disorder)

According to Barbaresi et al. (2005), an estimated 7% of school-age children have mathematics learning disorder (MLD). Children can encounter difficulties in math for a variety of reasons, and as a group children with MLD are highly heterogeneous. Diagnosis of MLD is typically based on underachievement on standardized measures of math achievement that contain an array of problem types. Therefore, two children with MLD may have very different patterns of strengths and weaknesses. Children with a history of language impairment (Fazio 1996; Young et al. 2002) or RD are also prone to having difficulties in math, with estimates of overlap between RD and MLD as high as 57%–64% (Barbaresi et al. 2005). Children with both RD and MLD tend to have lower math achievement and to progress in math skills more slowly than those with MLD alone (Jordan et al. 2003). This differentiation is important, because understanding the cognitive underpinning of MLD in both the combined RD-MLD and the MLD-only subtypes is essential to treating children with these disorders.

In a comprehensive review, Geary (2011) identified specific types of problems associated with MLD. First, children with MLD, and to a lesser extent those with persistent low achievement in mathematics, may have delays in fundamental number processing or representation systems. They lack a strong intuitive sense of numerical magnitude, which has been shown to be unrelated to intelligence or reading ability.

Second, children with MLD have a delay in the development of procedural knowledge characterized by difficulties executing math procedures such as counting strategies for addition or borrowing for subtraction (Geary 2011). In the early grades, these procedures include counting and learning the rules that underlie effective counting, such as knowing that the order in which items are counted is irrelevant. Children with MLD use more immature than atypical procedures, such as finger counting when solving simple arithmetic problems; show an incomplete understanding of underlying concepts in procedures; and make frequent execution errors. With support and continued instruction, children with MLD eventually tend to master the correct procedures, although much later than do their typically developing peers.

The third type of problem for children with MLD involves representing and retrieving number facts from long-term memory (Geary 2011). These number fact difficulties are associated with a high error rate and slow performance. Unlike the problems with procedural knowledge, which tend to improve with age, these memory problems tend to persist, even with extensive practice (Howell et al. 1987). Three mechanisms have been identified as potential contributors to these number fact retrieval deficits. First, given the association with both RD and language disorders (Fazio 1996), phono-

logical processing semantic systems have been posited as likely contributors. A two-factor model has also been proposed in which number sense, or a child's ability to understand number sequences and concepts, may underlie the number fact difficulties of children with only MLD, whereas weak phonological skills may underlie these difficulties in children with comorbid MLD and RD (Robinson et al. 2002). The second proposed mechanism underlying number fact retrieval involves deficits in working memory, and particularly in the ability to inhibit irrelevant information from disrupting number fact retrieval (Geary et al. 2012). This very specific form of working memory deficit is an important focus for interventions to help children with MLD number fact retrieval deficits despite their differences in other areas of ability including language skills and intelligence. Third, Geary (2011) proposed that deficits or delays in the development of basic number systems—in particular, the development of approximate magnitude representation system—may underlie number fact retrieval deficits in children with MLD.

In keeping with the differing demands of math problem solving across various ages and grades, interventions typically target a specific set or subset of skills. At the youngest ages, intervention is focused on preparatory arithmetic skills and number sense (Gersten et al. 2005). Interventions to enhance working memory skills should be included in programming for children with MLD. Repeated practice to improve number fact fluency and automaticity is also recommended.

Thorough assessment of an individual child's acquisition of basic number concepts and strategies is essential for targeting intervention appropriately. Improvements in more complex math problem-solving skills can be facilitated through the use of a highly structured program on problem-solving skills (e.g., problem content, labeling, computation). Effective intervention must explicitly teach rules for transferring solutions to novel problems and self-regulation of problem-solving performance (Fuchs et al. 2004). Learner characteristics play an important role in response to treatment, however, because children with combined MLD and RD have been found to respond less to this intervention than those with MLD alone (Fuchs et al. 2004). As with all other treatments for MLD, examination of learner characteristics is an essential first step before initiating any intervention. A recent article by van Garderen et al. (2012) outlines a variety of approaches to teaching mathematics to learners with MLD and recommends many links to Web sites that include resources for special educators.

Comorbid Disorders: Approach to Intervention

Children with LDs are at increased risk for other psychiatric disorders, including anxiety, depression, disruptive behavior disorders, and social difficulties that interfere with their functioning in a variety of domains. This increased risk for psychiatric disorders has been reported in both clinical and community samples (Beitchman and Young 1997; Young and Beitchman 2002) and is documented for a range of diagnoses, but the most extensive evidence relates to comorbidity with attention-deficit/hyperactivity disorder (ADHD).

There are conflicting reports of the degree of overlap between LD and ADHD, but recent estimates indicate that about one-third of children with ADHD will

also have an LD (DuPaul and Stoner 2003; DuPaul et al. 2013). Among LD students the prevalence of ADHD was estimated at 38%, or roughly seven times higher than the prevalence in the general population (DuPaul and Stoner 2003). Given the high degree of overlap between LD and ADHD, unless proven otherwise, it is necessary to screen for both conditions when a child presents with either one.

Internalizing disorders, particularly anxiety and depression (Boetsch et al. 1996; Maughan et al. 2003; Willcutt and Pennington 2000), frequently co-occur with LDs. Approximately 70% of students with an LD had more anxiety symptoms than non-LD students (Nelson and Harwood 2011). Furthermore, youths with poor reading ability were more likely to experience suicidal ideation or attempts and more likely to drop out of school than youths with typical reading (Daniel et al. 2006).

General Considerations

Given the known high rates of comorbidity among children with an LD, a comprehensive approach that addresses the child's learning needs and any associated comorbid psychiatric symptoms is necessary. An important corollary for successful treatment when comorbid behavioral or emotional difficulties are present is to help the parents and school appreciate the intimate connections between the learning problems and the child's behavioral and emotional problems. Notably, they need to understand that the child with an LD is not being lazy or apathetic or deliberately failing, but instead has a genuine disability for which he or she needs specific intervention and parental support. Response to treatment is enhanced when treatment between home and school is coordinated, so that parents and teachers are working closely together. Therapy can be better targeted when it is possible to distinguish those behavioral and emotional problems that arise due to the child's LD. For example, identifying the child's anxieties that are due to worries that he or she has not yet learned to read allows for focused interventions, such as reading remediation and psychotherapeutic support regarding self-concept and self-esteem.

LD With Comorbid Attention-Deficit/ Hyperactivity Disorder

Modifications of the classroom environment should always be considered in formulating treatment for children with LD and comorbid conditions. For the child with LD and ADHD, placing the child near the front of the class in clear view of the teacher and reducing the level of distractibility for the child are important components in the overall approach to intervention. Another option is to place the child in a small class, with an increased staff-to-child ratio. Specific behavioral strategies, including ignoring, praising, and token reinforcements, are also helpful (DuPaul 2007). Individual treatment of the child or adolescent should include goals of minimizing disability and maximizing potential through problem solving, social support, study habits, encouragement in extracurricular athletic or other activities, and help with further educational and career decisions.

For children with LD and concurrent ADHD, successfully treating the ADHD will usually lead to an improved response to the demands of the learning environment. Stimulant medication is the most effective treatment for ADHD (American Academy of Child and Adolescent Psychiatry 2002; Jensen et al. 2001;

Vaughan and Kratochvil 2012). Children with ADHD receiving stimulant medication were almost two times less likely to be retained a grade and had decreased school absenteeism and improved reading (Barbaresi et al. 2007).

Nevertheless, a study by Barnard-Brak and Brak (2011) revealed a statistically nonsignificant association between pharmacological treatment and academic achievement among children with ADHD. Although medication is not intended to treat the child's LD, medication to treat the comorbid ADHD is warranted. The choice, timing, and dose of medication will depend on the severity of the child's symptoms, the portion of the school day during which the symptoms interfere with classroom performance, and the size and weight of the child. Available stimulant medications for the treatment of ADHD are all derivatives of methylphenidate or amphetamine.

Pharmacotherapy for ADHD when that disorder is comorbid with an LD should be individualized for each child and requires evaluation of the dose response, duration of action, and tolerability of side effects. To optimize treatment, short-release, intermediate-release, and extended-release medications are available and should be titrated for optimal effect. To facilitate compliance, various administration options are available, such as capsules, sprinkle capsules, oral solution, and transdermal patches (Vaughan and Kratochvil 2012).

Recent drug formulations range from single-dose, immediate-release methylphenidate to a variety of new once-a-day, long-acting, extended-release formulations, which include Adderall and osmotic-release oral system (OROS) methylphenidate (Concerta) (American Academy of Child and Adolescent Psychiatry 2002). Although more expensive, these new stimulant formulations are easier for patients to use than older stimulants, are more resistant to abuse and misuse, and allow for increased privacy of ADHD treatment at school (Connor and Steingard 2004). Other medications, such as atomoxetine, have also been shown to be effective in the treatment of children with ADHD (Michelson et al. 2002, 2003) and would be considered second-line choices. However, with recent concerns about an increase in suicidal thinking, close clinical monitoring is essential.

Because ADHD is also commonly comorbid with other externalizing disorders such as oppositional defiant disorder and conduct disorder, comprehensive treatment options should be multimodal, including behavioral therapy and parent management training to help the family develop a supportive home environment and a consistent home-school reinforcement program; school consultation and academic interventions should be individualized to each case as appropriate (Hoza et al. 2008; Watson et al. 2012).

Remediating the LD may lead to improvements in behavioral symptoms in some children. Modifying academic expectations to be more in keeping with a child's current level of functioning may also assist in reducing the child's oppositional and acting-out behaviors. Finally, opportunities to pursue and develop athletic, musical, or other abilities can help improve the child's self-esteem and reduce acting-out behaviors.

LD With Comorbid Internalizing Disorders (Anxiety, Depression)

Identifying the source of the child's anxieties can be pivotal when planning treatment for a child with comorbid LD and

anxiety. The child may have performance anxiety, anxiety about speaking in front of the class, or anxiety about becoming a skilled reader. Teachers should be encouraged to be creative and make special arrangements. For example, the teacher might allow the child with LD who has a phobia about speaking in front of the class to instead do a video presentation.

When the child's anxieties are tied to his or her academic struggles, the child should receive psychotherapy to address the child's view of himself or herself as a competent learner, along with treatment to remediate his or her LD. It is important for the child to recognize that his or her academic struggles are understood and that help is on the way. Ensuring that the child's academic curriculum is properly attuned to his or her learning needs will also contribute to reducing the child's negative self-view.

Strong empirical evidence supports the use of psychotherapy as a first-line agent for anxiety disorders that are of mild to moderate severity. For symptoms that are more severe or impairing, research suggests the use of a combination of therapies, especially cognitive-behavioral therapy (CBT) plus antidepressants, in youths diagnosed with generalized anxiety disorder, social anxiety disorder, social phobia, and obsessive-compulsive disorder. The antidepressants fluoxetine and sertraline have both shown significant effects in the treatment of social anxiety disorder and generalized anxiety disorder (Peters and Connolly 2012).

Psychotherapeutic approaches, such as individual or group CBT for anxiety disorders, should be offered to children with continuing symptoms (Compton et al. 2004). Supportive-expressive group therapy has also been shown to be helpful (Leichtentritt and Shechtman 2010).

Emotional problems, including low self-esteem and elevated rates of depression and dysthymia, have also been associated with LD (Maughan et al. 2003). The treatment of the associated dysthymia or depression would include the use of CBT and other psychotherapeutic approaches as appropriate. Many depressed youths will respond to brief nonmedication supportive care given over a few weeks. When response to treatment is inadequate and antidepressant medication is recommended, a selective serotonin reuptake inhibitor (SSRI) is the primary psychopharmacological strategy.

SSRIs, in particular fluoxetine, should be considered for a child with comorbid depression whose depressive symptoms are unresponsive to psychosocial interventions (March et al. 2004). Fluoxetine and escitalopram have been approved by the U.S. Food and Drug Administration for use in adolescent depression (Choe et al. 2012). If the response to those medications is poor, citalopram and sertraline can be tried as second-line agents. Careful monitoring of the child's response to the medication is essential, given concerns regarding an increase in suicidality.

Conclusion

Direct treatment is warranted for concurrent psychiatric and other secondary emotional and social problems (Kauffman 1997). Studies suggest that children and adolescents with learning disorder who received specialized attention at school, support at home, and mental health services when warranted had the most positive outcomes (Osman 2000). Educational and clinical services must be coordinated and individualized to achieve the most effective outcome.

As children with LD mature into adolescence, they need to be assisted in learning to advocate for themselves because these skills will increase their chances of

success in adulthood. In treating adolescents, clinicians need to be aware of coexisting disruptive behavior disorders, mood and anxiety disorders, and substance use disorders, which may lead to school dropout, truancy, and delinquency (Beitchman et al. 2001a, 2001b). Prevocational and vocational skill development may be needed, and helping the family to evaluate the need and/or potential for postsecondary education is an appropriate role for the clinician (Scott 1994).

Taken together, the research literature demonstrates that the best approach to treating individuals with LDs involves early assessment and identification combined with evidence-based interventions and monitoring of progress over the course of development. Emphasizing each child's strengths and capitalizing on his or her interests is also important for maintaining self-esteem and ultimately enhancing the child's engagement with academic activities.

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CHAPTER 6

Tic Disorders

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DSM-5 (American Psychiatric Association 2013) criteria for Tourette's disorder mirror the description offered by Gilles de la Tourette (1885) more than 100 years ago (Box 6–1). A *tic* is defined in DSM-5 as a "sudden, rapid, recurrent, nonrhythmic motor movement or vocalization" (p. 81). As discussed in this chapter, DSM-5 details a spectrum of childhood-onset tic disorders, not attributable to another medical condition, that vary in duration from transient (lasting less than a year) to chronic (persisting more than a year) and according to whether only motor tics, only vocal tics, or both motor and vocal tics are present. (Unlike most other disorders in DSM-5, there are no severity or impairment thresholds required to make a diagnosis of a tic disorder.) When motor and vocal tics have been present and persisted at least a year, the term *Tourette's disorder* is used. These disorders are of psychiatric interest both because of the psychosocial impairment that the tics may cause and because of the comorbid conditions that may be associated with them.

Box 6–1. DSM-5 Diagnostic Criteria for Tic Disorders

Note: A tic is a sudden, rapid, recurrent, nonrhythmic motor movement or vocalization.

Tourette's Disorder **307.23** (F95.2)

A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).

Persistent (Chronic) Motor or Vocal Tic Disorder **307.22** (F95.1)

A. Single or multiple motor or vocal tics have been present during the illness, but not both motor and vocal.
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).
E. Criteria have never been met for Tourette's disorder.

Specify if:

With motor tics only
With vocal tics only

Provisional Tic Disorder **307.21** (F95.0)

A. Single or multiple motor and/or vocal tics.
B. The tics have been present for less than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).
E. Criteria have never been met for Tourette's disorder or persistent (chronic) motor or vocal tic disorder.

Definition, Phenomenology, and Natural History

Isolated, transient tics, lasting less than 1 year, are common in childhood, occurring in up to 33% of boys and 16% of girls in one classroom observational study of elementary school children (Snider et al. 2002). Motor or vocal tics that persist as long as 1 year are less common and are estimated to occur in 1.3%–3.7% of children. Prevalence estimates for Tourette's disorder (combined chronic multiple motor and vocal tic disorder) vary depending on whether one examines clinically ascertained cases or population-based samples (0.3%–0.8%). As is commonly the case in epidemiological studies, clinically ascertained cases have higher rates of co-occurring neuropsychiatric conditions than do cases identified in the general population, presumably because severity and comorbidity are among the factors bringing individuals to clinical attention (Scahill et al. 2013).

When tics first manifest in a youngster within the previous year, it is often impossible to predict whether they will prove to be transient or whether they will persist past 1 year and go on to warrant a diagnosis of either persistent (chronic) motor or vocal tic disorder or Tourette's disorder. Hence, within the first year of appearance, only a diagnosis of provisional tic disorder may apply. Clinical experience suggests that when multiple different types of tics are present, persistence may be more likely. In DSM-IV (American Psychiatric Association 1994), when tics were present for less than 1 year and then remitted and did not recur over subsequent years, the condition was termed *transient tic disorder,* but this category has been eliminated in DSM-5. Unlike many other conditions in DSM-5, there is no impairment or severity threshold for Tourette's disorder, persistent (chronic) motor or vocal tic disorder, or provisional tic disorder, and wide ranges

of severity, impairment, and comorbidity are found in affected individuals, ranging from severe cases to cases that may go largely unrecognized and never come to clinical attention.

To what extent the three tic disorders delineated by DSM-5, as described in Box 6–1, share common underlying genetic or other pathogenic factors is unclear. Within the pedigrees of probands with Tourette's disorder, it is common to see relatives who may have or have had only transient tics or persistent (chronic) motor or vocal tic disorder.

Simple motor tics are rapid, fleeting movements such as eye blinking, grimacing, or shoulder shrugging. *Complex motor tics* are more sustained, orchestrated, or semipurposeful movements such as touching, hopping, hitting oneself, or making obscene gestures out of context (copropraxia). *Simple vocal tics* consist of noises such as sniffing, throat clearing, coughing, or snorting. *Complex vocal tics* include repeating stock phrases such as "you bet" and "all right," repeating one's own phrases (palilalia), repeating others' words (echolalia), swearing or using obscene language out of context (coprolalia), and paroxysmal changes in volume.

Tics may be differentiated from other repetitive movements by characteristic features of suppressibility, premonitory urges, and variability. Other diagnoses to be considered are dystonia, myoclonus, chorea, seizures, athetosis, and stereotypies (Jankovic and Mejia 2006).

Tics are often preceded by premonitory urges and sensations (Leckman et al. 1993). Some individuals are able to spontaneously suppress troublesome tics at school or work, only to release them explosively at home. Even when individuals are able to suppress tics transiently, the premonitory urges and the struggle against them may be as onerous as the tics themselves.

Tics usually emerge during early or middle childhood, with the peak age at onset between 5 and 8 years (Bloch and Leckman 2009). In Tourette's disorder, initial motor tics usually consist of blinking or facial tics (such as grimacing), with subsequent rostral-caudal involvement of the shoulders, arms, trunk, or legs in more severe cases. Initial vocal tics usually involve sniffing or throat clearing that may be mistaken for allergies. Tics usually wax and wane in frequency and severity over hours, days, and months (Lin et al. 2002), with one tic often fading over time, only to have different tics make their appearance. Stress, excitement, fatigue, and illness can all exacerbate tic severity (Lin et al. 2007). Curiously, individuals with otherwise bothersome and disruptive tics sometimes report that the tics may be in abeyance during motor activities requiring sustained attention or coordinated or guided movements, such as musical or athletic performance.

Individuals with Tourette's disorder or persistent (chronic) motor or vocal tic disorder often show a wide variety of other subtle compulsive, repetitive, or "sticky" behaviors over and above the core, pathognomonic symptoms of persistent motor or vocal tics. Individuals with tics may be permeable to others' actions, a phenomenon that has been termed *somatic empathy*. In addition to having complex tics in the form of echopraxia and echolalia (compulsive repeating of others' actions or phrases), some people may experience suggestibility in that tics are triggered by discussing them in the course of history taking or by seeing or hearing others' tics. Complex tics may also involve repeating actions, utterances, or sounds until they look or sound "just right." Symmetrical touching or "touching back," evening up left and right, and repeating actions a certain number of odd or even times may be frequent or bothersome. Unlike compul-

sions seen in non-tic-related forms of obsessive-compulsive disorder (OCD), the repetitive behaviors in Tourette's disorder are motivated not by anxiety or harm avoidance, but by an intense feeling of discomfort (often straddling the mental and the physical) unless the action can be performed "just right."

The long-term course of tics in any individual is difficult to predict. As noted, many children have transient tics that may last only a few days or weeks. By definition, in Tourette's disorder and persistent (chronic) motor or vocal tic disorders, the tics have persisted at least 1 year (see Box 6–1). In Tourette's disorder, early adolescence is often the period of greatest severity, with a spontaneous diminution or disappearance of tics by early adulthood in a majority of cases (Bloch and Leckman 2009). However, even when the tics have improved, comorbid OCD, attention-deficit/hyperactivity disorder (ADHD), and anxiety proneness may persist unabated. The natural history of persistent (chronic) motor or vocal tic disorder, as distinct from Tourette's disorder, has been little studied.

The causes of persistent tic disorder and Tourette's disorder are unknown but appear to be largely genetic, with environmental factors such as perinatal adversity and maternal smoking providing early risk factors and infectious or autoimmune factors perhaps playing a role in a minority of cases in childhood. Several genes of interest have been identified, but it appears likely that the disorders will prove to be polygenetic and heterogeneous—that is, requiring the interaction of multiple genes, with perhaps different genes playing a role in different families.

The pathophysiology of the persistent tic disorders likewise remains unknown but is the object of intense research efforts. Dysregulation of cortico-striato-thalamic circuits appears to be the central defect. Elucidation of these defects, one can hope, will lead in time to more effective means of pharmacological, behavioral, and neuromodulatory therapeutic intervention.

Several recent comprehensive reviews and guidelines provide detailed overviews of the phenomenology, pathophysiology, assessment, and treatment of tic disorders (Cath et al. 2011; Martino and Leckman 2013; Murphy et al. 2013; Pringsheim et al. 2012; Roessner et al. 2011; Steeves et al. 2012).

Comorbid Conditions

Several comorbid conditions frequently accompany tic disorders and must be addressed in assessment and treatment planning, because they often cause more distress or impairment than the tics themselves. Difficulties with inattention, impulsivity, and/or irritability are found in about half of patients referred for treatment (Sukhodolsky et al. 2003). Obsessions and compulsions are found in up to two-thirds of individuals with tics or Tourette's disorder (Lewin et al. 2010). Individuals with Tourette's disorder also appear to be at increased risk for anxiety (Coffey et al. 2000), depression, and neuropsychological impairments in fine motor coordination, visuomotor integration, and executive functioning that may impair academic performance, especially in those with comorbid ADHD (Gorman et al. 2010; Khalifa and von Knorring 2006).

Initiation of Treatment

Treatment planning for Tourette's disorder requires an awareness of development, neurobiology, life events, social

context, and intrapsychic processes at work in the patient and family. The clinician's task is to identify the principal sources of the patient's (and family's) distress and impairment, as well as potentially exacerbating or ameliorating factors, in order to prioritize the goals and targets of intervention. Successful treatment requires coordinating different simultaneous interventions that target these elements. Thus, the assessment of patients for Tourette's disorder extends beyond determining the mere presence or severity of tics and includes evaluating the patient's functioning in a variety of domains, including school, peers, self-image, future aspirations, and relationships with family members (King and Landeros-Weisenberger 2013).

To assess tics, the clinician needs to ascertain their location, frequency, and intensity; the degree of distress and impairment they produce; and whether premonitory urges occur with movements. Standardized rating scales for quantifying these dimensions are available, utilizing clinician ratings based on a semi-structured interview (Yale Global Tic Severity Scale [YGTSS]) or a visual analog scale (Hopkins Motor and Vocal Tic Scale [HMVTS]); parent- and self-report formats are also available. Other instruments permit severity ratings from video samples (these are influenced by the situational aspects of the sample). The Premonitory Urge for Tics Scale (PUTS) is a specialized scale focusing on the subjective experiences of premonitory urges that precede tics, which can contribute to distress and impairment and are important in planning behavioral interventions, such as Habit Reversal Therapy (see section "Psychological and Environmental Interventions" later in this chapter). Details of tic assessment, including standardized instruments for rating severity, are available elsewhere (Cavanna and Pansaon Piedad 2013; King and Landeros-Weisenberger 2013).

The goal of assessment is to learn as much as possible about factors that influence the patient's symptoms and to determine which symptoms are the most onerous. For some patients, tics and their accompanying premonitory urges are the greatest burden; for others, comorbid obsessions, compulsions, anxiety, irritability, inattention, or learning impairment may be the most problematic. In addition, individual patients and their families, peers, and school environments may differ widely in their ability to tolerate or accommodate a given symptom problem. It is therefore also crucial to assess how the child's symptoms interact with any coexisting psychological difficulties, family tensions, and peer or school difficulties, which may not only be impairing in their own right but also further exacerbate tics and anxiety, thereby perpetuating a vicious cycle. Such information is essential for selecting and monitoring treatment interventions.

Treatment Interventions

General Considerations

The primary goal of treatment for a tic disorder is to facilitate a patient's developmental progress by providing active support and reducing as many impediments to healthy developmental progress as possible. Appropriate treatment planning also seeks to minimize additional impairment from other sources such as medication side effects, spiraling family anxiety, academic difficulties, and social isolation. The clinician must be alert to the changing demands that these chronic disorders place on patients and families. The burden of illness may vary with the patient's phase of development. For ex-

ample, with adolescence, prominent tics or medication-associated weight gain may pose new social problems to which the youngster is acutely sensitive. On the other hand, by the college years, peer teasing and ostracism usually diminish as patients' other assets and competencies become more socially salient.

Psychological and Environmental Interventions

Patient and Family Education

Patient and family education is a mainstay of treatment for tic disorders. Education about the etiology and natural history of the disorder and available treatment is imperative. Education can reduce anxiety, put symptom severity in perspective, and lay the groundwork for more specific interventions. Advocacy organizations such as the Tourette Syndrome Association (www.tsa-usa.org) and the New Jersey Center for Tourette Syndrome (www.njcts.org) can be very helpful in providing psychoeducational resources, support groups, and referral lists of local experienced clinicians, educational consultants, and advocates.

School-Based Interventions

In addition to having social problems and disruptions caused by tics, many children with Tourette's disorder, especially those with comorbid ADHD, have coexisting learning problems due to difficulties with visual-motor and visual-spatial integration, graphomotor skills, and executive functioning and organizational capacities. Standardized psychological evaluations can help identify these problems and guide individualized educational planning (Murphy and Eddy 2013). Clinicians must work closely with school staff. Educating teachers and school nurses about Tourette's disorder is a vital first step in the care of an individual patient. Children with high levels of impulsivity, inattention, and restlessness require classroom programming that is predictable, articulates clear expectations, has low pupil-to-teacher ratios, and contracts for rewards within time frames that are consonant with the patient's limitations. For children and adolescents with severe motor tics, modifications such as use of word processors, permission to take extra time for examinations or use a separate room, ability to leave the classroom briefly when tics are severe, and resource help in organizing assignments may also be useful (Packer 2005). School staff should pay attention to these children's relationships with classmates and try to minimize subtle or overt exclusion. Social isolation and ostracism can be ameliorated by educating students about Tourette's disorder in small groups or in the entire class.

Behavioral and Other Interventions at Home

Severe symptoms—whether of tics, obsessions and compulsions, and/or impulsivity—often create a vicious cycle of increasing stress, increasingly severe symptoms, and increasing impairment at home as well as at school. Many of the strategies that are useful in school may be applied at home, especially those for impulsivity, inattention, and hyperactivity. Taking the time to develop behavioral programs with clear expectations, predictability, and appropriate and timely rewards for achievement can be extremely helpful.

When youngsters have both tics and disruptive behaviors, parents may have difficulty with appropriate limit setting, due to confusion as to which behaviors

are tics to be tolerated and which are impulsive behaviors that require structure, consistent expectations, and consequences. The clinician can provide useful guidance to parents in clarifying such issues as well as in implementing effective behavioral management techniques (Scahill et al. 2006a; Sukhodolsky et al. 2009).

Individual Psychotherapy

The adaptation some patients make to their symptoms may have dramatic effects on interpersonal relationships. Battles over dependency and autonomy, oppositional behaviors, risk taking, and investment in being seen as "sick" or helpless are examples of detrimental patterns that can entangle others. Although individual psychodynamic psychotherapy cannot decrease tics per se, it may assist patients who develop such highly maladaptive concessions to their illness, as well as reduce potentially tic-exacerbating stress. Serious comorbid conditions, such as anxiety or depression, may aggravate tics and require interpersonal or cognitive psychotherapy in their own right.

Family Therapy

Tourette's disorder can place an extraordinary burden on family relationships. Tourette's disorder symptoms influence and are influenced by the family system; recognizing this reciprocal relationship between symptoms and family functioning is important. Impaired family relationships can fuel stress at home. Destructive parent-child dynamics can crystallize around the nidus of tic symptoms and serve to limit or thwart improvement.

Specific Behavioral Therapies for Tics

Since the seminal work of Azrin and Nunn (1973), considerable progress has been made in adapting Habit Reversal Therapy (HRT) for management of tics. HRT is a behavioral treatment that consists of 1) self-monitoring to increase awareness of premonitory urges, 2) training patients to develop and implement competing responses that are incompatible with the tics, 3) relaxation training, and 4) contingency management (Piacentini and Chang 2005). HRT has been evaluated in several small-size randomized studies that showed its effectiveness for reducing tics (Azrin and Peterson 1990; Deckersbach et al. 2006; Verdellen et al. 2004; Wilhelm et al. 2003). More recently, HRT has been integrated as a core component into a structured, manualized Comprehensive Behavioral Intervention for Tics (CBIT) (National Tourette Syndrome Association 2014; Woods et al. 2008).

CBIT was recently evaluated in two large randomized controlled trials (RCTs), one in children ages 9–17 (Piacentini et al. 2010) and another in adults with Tourette's syndrome (Wilhelm et al. 2012). Compared with subjects in the supportive therapy and education control condition, subjects receiving CBIT showed clinically and statistically significant decreases in tic severity.

During HRT, individuals with Tourette's disorder are asked to detect the initial signs of a premonitory urge and then to perform a competing response instead of the tic until the premonitory urge dissipates. The primary components of HRT are tic awareness and competing-response training. Tic awareness training entails self-monitoring of current tics, focusing on the premonitory urge or other early signs that a tic is about to occur. Competing-response training is based on the observation that performance of a tic results in a decrease in the premonitory urge; involves engagement in a voluntary behavior physically in-

compatible with the tic, contingent on the premonitory urge or other signs of impending tic occurrence; and is distinct from deliberate tic suppression in that it teaches the patient to initiate a specific voluntary movement when he or she notices that a tic is about to occur. Initially, patient and therapist create a tic hierarchy, ranking tics from most to least distressing, and plan to address more distressing tics earlier in treatment. Awareness training and competing-response training are then implemented and practiced one tic at a time. For example, a child with a neck-jerking tic may be taught to look forward with his chin slightly down while gently tensing neck muscles for 1 minute or until the urge goes away. Current guidelines suggest that the competing response does not have to be physically incompatible with the targeted tic to be effective and that any voluntary movement can reduce the desire to perform the tics. This observation is consistent with the commonly reported reduction of tics during periods of goal-directed behavior, especially those that involve both focused attention and fine motor control, as occur in musical and athletic performances.

In addition to awareness training and competing responses, CBIT includes functional-based assessment and intervention. The purpose of functional assessment is to identify situational factors that may contribute to the performance or worsening of tics. Adding functional assessment as a CBIT component was based on the observations that tics can be worsened by specific situations such as being in public and activities such as watching TV (Conelea and Woods 2008). Functional assessment is conducted on a tic-by-tic basis using a checklist of antecedents and consequences that may be associated with tic worsening. Examples of tic antecedents include situations such as "at home after school" and "during meals." Examples of consequences include "does not complete meal or homework" and "gets to stay up late." Functional assessment is conducted in an interview with parent and child, and the clinician asks whether each of the antecedent and consequence items is associated with improvement or worsening of each tic. Upon completion of the assessment, an intervention plan is developed for tics that have identifiable situational factors. For example, if a child's throat-clearing tics become more frequent during mealtimes and are associated with siblings' comments and requests to stop, a functional intervention may include asking the child with tics to practice a relaxation exercise for several minutes before dinner and explaining to the siblings that their reactions may inadvertently strengthen the tics. Particular attention is given to evaluating and, if needed, eliminating opportunities for escape and avoidance conditioning because tics may be reinforced by escaping unpleasant situations. For example, if vocal tics were to exacerbate every time dinner included a healthy serving of vegetables, and the child were to be excused from the table and allowed to dine on snack food, a function-based intervention would include revising the menu so that it is more acceptable and eliminating positive consequences of not eating the dinner. Because stress may be associated with exacerbation of tics (Lin et al. 2007), relaxation training is often used as an auxiliary technique to manage worsening of tics that may be triggered by situational anxiety. Finally, behavioral reward systems can be used to encourage children's engagement in HRT and practicing tic management strategies at home.

Because younger children are often unaware of premonitory urges, it usually makes sense not to offer HRT unless the

child can clearly identify these sensory urges. In addition, motivation to better control tics and the ability to form a working alliance around that task are prerequisites for successful HRT. More work is needed to identify predictors of treatment response to HRT and to develop flexible treatment protocols that can also address tic-related obsessions and compulsions.

Behaviorial Therapies for Rage and Disruptive Behavior

Disruptive behaviors such as anger outbursts, aggression, and noncompliance have been reported in up to 60% of clinical samples and 40% of community samples of children with Tourette's syndrome (Khalifa and von Knorring 2006; Scahill et al. 2006b). The intensity and unpredictability of anger outbursts in response to minimal provocation have prompted appellations such as *rage attacks* or *rage storms* (Budman et al. 2003). In many cases, disruptive behavior may be a source of greater impairment than tics (Sukhodolsky et al. 2003). Consequently, assessment and management of disruptive behavior should be an important part of treatment for children and adolescents with Tourette's disorder. Despite the increasing appreciation for disruptive behavior problems in Tourette's disorder, there have been few systematic efforts to apply psychosocial treatments that have been well established for children with disruptive behavior disorders to children with Tourette's disorder. (See Part IX, "Disruptive, Impulse-Control, and Conduct Disorders," for discussion of treatment of childhood disruptive disorders.) Two recently completed RCTs have examined the efficacy of behavioral interventions adapted to target disruptive behavior in youngsters with Tourette's syndrome. The first study evaluated the effectiveness of Parent Management Training (PMT) in children with chronic tics (Scahill et al. 2006a). The second study evaluated cognitive-behavioral therapy (CBT) for anger control in adolescents with Tourette's syndrome (Sukhodolsky et al. 2009).

PMT is a psychosocial treatment in which parents are taught skills for managing their children's disruptive behavior and has proven effective in numerous clinical trials in children with disruptive behavior (Kazdin 2005). The broad goals of PMT are to improve parental competence in dealing with child behavioral problems and to improve the child's adaptive behavior. Some of the parenting skills include frequent praising of appropriate behavior, communicating directions effectively, and being consistent with consequences for disruptive behaviors. PMT targets those parent-child interactions that have been shown to foster disruptive behaviors. Behaviors such as noncompliance, whining, or bickering can be reinforced if they result in escape or avoidance of situations, such as homework or room cleaning, that could be aversive to the child. In contrast, positive reinforcement of desirable behaviors, such as brushing teeth, doing homework, or sharing toys with siblings, is at the core of PMT. However, discussions with parents often reveal that they may inadvertently give attention to disruptive behavior and fail to praise appropriate behavior. Hence, PMT offers structured education and exercises that enable parents to learn and implement specific techniques for reducing behavioral problems.

A specific adaptation of PMT for children with tic disorders complicated by disruptive behavior was studied in a 10-week RCT (Kazdin 2005). Before treat-

ment, all the children showed moderate to severe levels of oppositional and defiant behavior. Compared with those receiving treatment as usual, the children assigned to the PMT program showed significant improvement in disruptive behavior as rated by parents and a clinician rater blind to treatment assignment. These results suggest that PMT is helpful for short-term improvement in disruptive behavior problems in children with tic disorders.

CBT for anger and aggression is another behavioral intervention that has been well studied in children with disruptive behavior disorders (Sukhodolsky and Scahill 2012). In contrast to PMT, which is conducted with the parents, CBT is conducted with the child to improve social-cognitive skills for dealing with conflicts and frustration. CBT consists of structured, weekly sessions that include education about emotion regulation, problem-solving training, and role-playing of appropriate behavior in frustrating situations. For example, as part of problem-solving training, the child has to identify and evaluate the consequences of various actions for himself or herself and for the others involved in hypothetical conflicts. After that, the child can be asked to recall a time when he or she was frustrated and to problem-solve and role-play behaviors that would have prevented or reduced his or her frustration. At the end of each session, the child is assigned homework to practice particular "anger coping" skills and to write about his or her positive anger-management experience.

A specific adaptation of anger-management CBT for adolescents with Tourette's syndrome complicated by disruptive behavior and explosive outbursts was evaluated in a 10-week RCT (Sukhodolsky et al. 2009). Before treatment, all children showed moderate to severe levels of oppositional and defiant behavior. At the end of treatment, compared with the treatment-as-usual group, the youngsters in the anger-management group showed a significant decrease in disruptive behavior, as rated by parents and a clinician blind to treatment assignment. These results suggest that anger-management training is helpful for short-term improvement in disruptive behavior problems in older children and adolescents with tic disorders.

Pharmacological Therapies

The use of pharmacological agents in the treatment of tics and associated symptoms has received extensive attention over the last three decades. Medications should be prescribed in the context of a therapeutic relationship in which the patient and family understand the symptom targets for which the drug is being used and are able to communicate about any side effects or concerns. The decision to prescribe should be the outcome of a careful discussion weighing the level of impairment, potential risks, and possible benefits (Scahill et al. 2011). Several important principles guide the use of medication in treating Tourette's disorder (Scahill et al. 2011):

1. The goal for pharmacological treatments for tics is to minimize impairment, not to eliminate tic symptoms completely.
2. Medication should be started at the lowest dosage possible, and the dosage can be gradually raised in small increments after ensuring an adequate duration to judge response.
3. The lowest effective dosage should be maintained to prevent side effects.
4. Polypharmacy should be minimized to the extent possible.
5. Only one medication should be added or discontinued at a time.

6. Medications should be tapered very slowly to avoid rebound exacerbation of tics.
7. Tics wax and wane in severity. Exacerbations in tic severity are common, especially during periods of stress and fatigue. Pharmacological treatments for tics do not need to be adjusted during each short-term symptom exacerbation.
8. Tics typically reach their worst severity between 10 and 12 years of age and often improve during adolescence (Bloch and Leckman 2009). Children can be tapered off medications slowly during periods of low stress if they have minimal tic symptoms.

Pharmacotherapy for Tics

Indications for pharmacological treatment of tics are physical discomfort, distress, interference with classroom functioning, and social stigma. The goal of treatment is reducing tic intensity to a tolerable level; attempting to suppress tics completely is often futile and risks overmedication, with attendant sedation or other side effects.

Pharmacological agents that have been shown to be useful in the treatment of tics include the α_2-adrenergic agonists and typical and atypical antipsychotics. Even though the antipsychotics are the most effective pharmacological agents for reducing tic severity, α_2 agonists are generally recommended as a first-line treatment for tics because of their more benign side-effect profile (Scahill et al. 2001). The usual total daily dose of guanfacine is 1–3 mg taken in two to three divided doses; the usual total daily dose of clonidine is 0.1–0.3 mg taken in three to four divided doses. Newer longer-acting formulations of both guanfacine and clonidine are currently available and are likely similarly effective in reducing tic severity. However, the effective daily dose range should be determined initially on the shorter-acting formulation. The principal side effect is dose-related sedation. Hypotension is usually not a problem with careful dosing. It may take several weeks to see the full effect of the α_2-adrenergic agents.

For persons for whom the α_2-adrenergic agonists are not sufficiently effective or well tolerated, a trial of a neuroleptic is indicated if the tics are sufficiently bothersome to warrant medication. For the treatment of Tourette's disorder, haloperidol and pimozide have been studied more than any other agents. Of the older typical antipsychotics, fluphenazine is used by some clinicians. Tardive dyskinesia is rare in children taking low doses of antipsychotics for relatively brief periods of time. Nevertheless, parents' (and clinicians') concerns about the theoretical risk of tardive dyskinesia have led to increased use of the newer atypical antipsychotics for tic disorder. Of these medications, only risperidone and ziprasidone have been shown to be useful for tics in controlled studies (Weisman et al. 2013). There is also some initial evidence supporting the use of aripiprazole for some but not all patients with Tourette syndrome (Wenzel et al. 2012). (It should not be assumed that all atypical antipsychotics are useful for tics, given that the paradigmatic atypical antipsychotic clozapine has been shown to have no benefit for tics and even to increase their severity.) Despite their theoretical advantage of a lower risk of tardive dyskinesia, the atypical antipsychotics share all of the troublesome short-term side effects of the older typical antipsychotics (i.e., sedation, cognitive blunting, acute extrapyramidal symptoms, and medication-induced separation anxiety) and, in the case of risperidone and olanzapine, marked weight gain and associated metabolic problems. Head-to-head trials have

failed to demonstrate any differences in efficacy between the antipsychotics commonly used for tics (Weisman et al. 2013). Careful electrocardiographic monitoring for QTc prolongation is essential with pimozide and ziprasidone, and caution is necessary regarding coadministration of medications that may interfere with cytochrome metabolism (e.g., macrolide antibiotics, some selective serotonin reuptake inhibitors [SSRIs]), which can result in fatal arrhythmias.

Perhaps 80% of patients with Tourette's disorder will benefit from haloperidol or pimozide, with a mean reduction of symptoms of 65%. However, haloperidol, fluphenazine, and pimozide produce significant adverse effects, especially sedation or cognitive blunting, with up to 50% of patients developing side effects. For some patients, the side effects are as intolerable as their tic symptoms and often lead to medication discontinuation. Hence, it is important to aim for the lowest possible dosage of medication and to remain vigilant for sedation and cognitive blunting in children taking antipsychotics (Scahill et al. 2011).

Other dopaminergic agents proven useful for tics but not approved for use in the United States include tiapride and sulpiride. Tetrabenazine is a dopamine inhibitor, recently approved in the United States for the treatment of the chorea of Huntington's disorder; it has also proved useful in tic disorder, albeit with dose-related side effects of depression and sedation (Chen et al. 2012).

A variety of medications have been tried for individuals with tics who are unresponsive to the usual medications (antipsychotics, α-adrenergic agents). In small open pilot trials, a variety of agents have appeared to be equivocally useful for tics, sometimes in combination with antipsychotics (Murphy et al. 2013; Roessner et al. 2011; Swain et al. 2007). These agents include calcium channel antagonists such as donepezil; dopaminergic modulators such as levodopa, ondansetron, and naltrexone; the antiepileptic drugs topiramate (Jankovic et al. 2010), valproate, and levetiracetam; and various nutritional supplements (Kompoliti et al. 2009). Data regarding these tertiary agents are more fragmentary and difficult to generalize.

Botulinum toxin injection may be useful for reducing severe specific localized tics (e.g., eyelid or vocal tics) but does not produce improvement of tics at untreated sites (Marras et al. 2001). Possible side effects include bothersome muscle weakness. If effective, injections must be repeated every 3 months or so.

Pharmacotherapy for Obsessive-Compulsive Symptoms

OCD symptoms are common in individuals with Tourette's disorder, even when their tics are not troublesome. The treatment of OCD is reviewed elsewhere in this volume (see Chapter 21, "Obsessive-Compulsive Disorder"). The SSRIs have been shown to be effective in children with OCD; however, the presence of a comorbid tic disorder has been an exclusionary criterion for many clinical trials. This is unfortunate because tic-related forms of OCD differ from non-tic-related OCD in several respects, including phenomenology and responsiveness to SSRIs. Tic-related OCD is less responsive to SSRI monotherapy than is non-tic-related OCD (March et al. 2007) and may require augmentation by the addition of a neuroleptic (Bloch et al. 2006). The SSRIs are generally well tolerated in individuals with comorbid tics and OCD, with the most common side effect in children being behavioral activation. Adverse drug interactions must be watched for

when antipsychotics and SSRIs are being coadministered.

Pharmacotherapy for Impulsivity, Inattention, and Hyperactivity

The treatment of ADHD-like symptoms in children with tics has been a source of controversy and the focus of much clinical research over the past 15 years. The U.S. Food and Drug Administration (FDA) currently requires the package inserts of most psychostimulant medications to list the presence of a tic disorder or a family history of Tourette's syndrome as a contraindication to their use. Among individuals with ADHD-like symptoms and tics, case reports have suggested that the use of psychostimulant medications may cause de novo tics or worsen existing tics. On the other hand, several lines of evidence suggest that the association between psychostimulants and tics may to a large extent be a result of confounding factors.

Approximately 20% of children with ADHD develop a chronic tic disorder. When tics and ADHD co-occur, symptoms of ADHD typically precede the onset of tic symptoms by 2–3 years; thus, a proportion of children diagnosed initially with ADHD may have or will develop previously undiagnosed tic symptoms. From these data, one would expect a substantial proportion of children diagnosed with ADHD to develop tics regardless of treatment. This observation limits the ability of case reports or observational data to establish a causal association between psychostimulant use and tics. Indeed, carefully controlled trials and a meta-analysis have failed to demonstrate worsening of tics with psychostimulant treatment for ADHD in children with both conditions (Bloch et al. 2009; Tourette's Syndrome Study Group 2002).

Because of the FDA warning and because some children will experience new onset or exacerbation of tics while taking psychostimulants, the clinician must weigh the relative impairment caused by the child's ADHD against the risk of possibly increased tics. For children with mild tics but significantly severe ADHD, the ADHD symptoms may be far more academically and socially impairing than the tics.

Our own preference in cases of comorbid ADHD and tics is to begin with one of the α_2-noradrenergic agonists (guanfacine or clonidine), which are helpful both for reducing tics and for controlling ADHD symptoms (Bloch et al. 2009; Tourette's Syndrome Study Group 2002). The utility of the α-agonists for tics appears greatest in patients with both tics and comorbid ADHD. The α-adrenergic agents are usually well tolerated in low dosages. Sedation can be a problem as the dose increases. Guanfacine, which is longer acting, may have greater affinity than clonidine for critical frontal region receptors, with greater benefit for inattention and less sedation. If α_2-noradrenergic agents are not successful, alternatives include a cautious trial of a stimulant or another nonstimulant agent.

Atomoxetine, a nonstimulant, has proven useful for ADHD in children both with and without tics. Although a large case series did not observe an increase of tics with atomoxetine in children with comorbid ADHD and tics, there are case reports of children whose tics do exacerbate when taking this medication (Bloch et al. 2009).

Tricyclic antidepressants, such as desipramine and nortriptyline, have been found to be beneficial in the control of hyperactivity and impulsivity in children with tics and ADHD without exacerbating tics (Bloch et al. 2009), but these medications may pose a serious risk of cardiac

arrhythmia in some children. Hence, use of the tricyclic antidepressants requires close electrocardiographic monitoring and careful attention to dosing and potential drug-drug interactions.

Some patients are forced to confront worsening tics when stimulants are the only agents that reduce their ADHD-like symptoms. The transient addition of an antipsychotic or α-adrenergic agent may temporarily be necessary under these circumstances.

Experimental Therapies

Neurosurgery has been used for severe, intractable, incapacitating tics that are unresponsive to more conservative interventions. Over the past decade or so, in patients with severe treatment-refractory Tourette's disorder, chronic high-frequency deep brain stimulation via stereotactically implanted bilateral subthalamic electrodes has produced dramatic symptom improvement with only minor side effects (Steeves et al. 2012). At present, this is an experimental procedure that should be used only in adult patients who are severely affected and whose symptoms have been resistant to other treatments. Further research is needed to delineate optimal patient selection, loci for electrode placement, and stimulus parameters.

Conclusion

With recent research that implicates dysregulation of cortico-striato-thalamocortical pathways in the pathogenesis of Tourette's disorder, magnetic resonance imaging (MRI) evidence linking basal ganglia features to tic severity and prognosis (Bloch and Leckman 2009), and increasingly powerful methods for studying the genetic determinants of these disorders, researchers are on the threshold of discovering basic relationships among genes, neurocircuitry, and clinical symptoms. These advances promise to yield more specific medications, treatment techniques, and accurate genetic counseling.

Clinicians, families, and patients must wrestle with the day-to-day impact of symptoms. Forming and maintaining a close physician-patient relationship, educating the patient and family about Tourette's disorder, and implementing school-based interventions continue to be critical in this struggle. An expanding variety of medications are now available to help patients, if used carefully to avoid burdensome side effects. Great progress has been made in developing new behavioral methods of intervention. Nevertheless, the cornerstone of treatment firmly remains with the clinician acquiring an understanding of the person with the disorder and being mindful of his or her specific talents, aspirations, and needs.

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Useful Web Sites

Tourette Syndrome Association: www.tsa-usa.org

New Jersey Center for Tourette's Syndrome: www.njcts.org

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CHAPTER 7

Elimination Disorders

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Disorders of bladder and rectal function leading to dysfunctional elimination of urine and feces are common in children, are often comorbid with psychiatric or neurological conditions, and in many cases persist into adulthood. Despite their clinical prevalence and substantial psychosocial and developmental morbidity, these conditions remain relatively poorly understood and therefore are often clinically missed or undertreated. The terminology used to describe these disorders is one indication of our lack of sophistication: although the bladder and bowel are complex organs that serve functions of both storage and elimination, only elimination is accounted for in the diagnostic nomenclature.

Several biological systems are intricately involved in normal storage and elimination of urine and feces. In addition to the genitourinary (GU) and gastrointestinal (GI) systems, the central and peripheral nervous systems play important roles in normal elimination and storage processes. The interplay between these systems can in part explain the high comorbidity between elimination and psychiatric or psychological disorders, which further complicates the diagnosis and treatment of these disorders (Baeyens et al. 2007; Cortes et al. 2012; Franco 2011b; Hyde et al. 2008).

The fact that the GU systems of boys and girls differ adds yet another layer of complexity that impacts diagnosis and treatment. Moreover, the close interplay between GU and GI functioning in the area of storage and elimination serves as a confounding issue for many treating clinicians. Finally, the psychological and emotional backdrop upon which these disorders present is important in both identification and treatment. This chapter focuses predominantly on dysfunctional elimination; we briefly address issues of etiology and then discuss how all these factors together impact diagnosis and treatment.

Developmental Considerations

Evolutionarily, the function of voiding urine or feces is a necessity of many living organisms. The way in which these functions occur has limited impact on the nonhuman organism, as long as they occur with regularity; only the inability to eliminate waste is dysfunctional, because it confers physiological consequences. Human beings, however, have sets of social and cultural norms around the act of elimination, and elimination outside of these norms or expectations is considered disordered.

Appropriate development from a young human to an adult lies in the act of acquiring skills or learning behaviors necessary to function independently in society as an adult. Sociologically, successful functioning as an independent adult includes having total control of bladder and bowel, whether awake or asleep. Typically, this control occurs roughly between ages 2 and 4 years, commensurate with the developmental readiness of the individual child (Kaerts et al. 2012).

Coordination of storage and voiding of urine and feces is a complicated interplay of neurological centers, peripheral nerves, and neurotransmitters. The frontal cortex activation center communicates with the voiding center (Barrington's nucleus) both directly with corticotropin-releasing factor and indirectly through the locus coeruleus with norepinephrine. The midpons micturition center communicates through the sacral nerve center and down afferent limbs to the detrusor and rectal smooth muscle and stretch receptors (Reiner 2010). At resting state, the bowel and bladder are receptacles that store feces and urine; as the bowel and bladder fill, stretch receptors lead to detrusor or rectal contraction that must be intimately coordinated with sphincter relaxation to expel the contents.

When a child has difficulty with elimination, clinicians must identify the specific area of dysfunction for appropriate treatment. Elimination disorders have been oversimplified in the past, causing practitioners to choose inappropriate treatments. The anatomical differences between boys and girls add further confusion to issues of diagnosis and treatment of dysfunctional elimination. This sex difference in elimination is further complicated by the complex interplay between bowel and bladder systems, as discussed in the subsections "Evaluation" and "Management" later in this chapter. Specific screening questions and straightforward guidelines are presented here to provide psychiatrists the knowledge to evaluate and more accurately diagnose and more appropriately treat elimination disorders and related aspects of development (Kaerts et al. 2012).

Enuresis

The term *enuresis* is derived from the Greek root word *enourin,* meaning "to void urine." In DSM-5 (American Psychiatric Association 2013), *enuresis* is defined as either involuntary or intentional voiding of urine into clothing or bed. To be considered pathological, the behavior must occur at least twice a week for at least 3 months. Importantly, the diagnosis can be considered for any frequency of enuretic behavior that causes significant psychosocial dysfunction and impairment. The behavior should not be due to other medical conditions, such as infections or neurological or anatomical problems, or to the use of medications or

substances. Age at onset (chronological or intellectual) should be at least 5 years. The disorder is subcategorized as nocturnal only, diurnal only, or both (Box 7–1).

Box 7–1. DSM-5 Diagnostic Criteria for Enuresis

307.6 (F98.0)

A. Repeated voiding of urine into bed or clothes, whether involuntary or intentional.
B. The behavior is clinically significant as manifested by either a frequency of at least twice a week for at least 3 consecutive months or the presence of clinically significant distress or impairment in social, academic (occupational), or other important areas of functioning.
C. Chronological age is at least 5 years (or equivalent developmental level).
D. The behavior is not attributable to the physiological effects of a substance (e.g., a diuretic, an antipsychotic medication) or another medical condition (e.g., diabetes, spina bifida, a seizure disorder).

Specify whether:

Nocturnal only: Passage of urine only during nighttime sleep.
Diurnal only: Passage of urine during waking hours.
Nocturnal and diurnal: A combination of the two subtypes above.

In contrast to DSM-5, the International Children's Continence Society (ICCS) restricts use of the term *enuresis* to nighttime wetting only rather than using the term to broadly define this category; the idea behind this restricted use is that nighttime wetting is inherently involuntary, whereas daytime wetting may be voluntary or involuntary. ICCS further characterizes daytime incontinence as including dysfunctional voiding, urinary frequency, and dysuria, all of which are necessary to consider in determining etiology and appropriate treatment (Nevéus 2010). *International Statistical Classification of Diseases and Related Health Problems,* 10th Revision (ICD-10) criteria require at least two episodes of wetting per month for children ages 5–7, and at least one episode per month for children age 7 and older (World Health Organization 1992). Enuresis historically has been considered either primary (the child has never attained continence) or secondary (the child had continence for a period of 6 months before incontinence returned), although it is not clear whether this distinction is clinically useful. Finally, there is disagreement about whether the DSM-5 criteria (see Box 7–1) are fully representative of this class of disorders (von Gontard 2013). Specifically, the term *impairment* is not fully defined, and specific symptoms and symptom severity are not detailed. The distinction of diurnal occurrence may be relevant to etiology and therefore treatment, because overactive detrusor, reduced bladder volume, or relative nighttime vasopressin deficiency may be implicated in nighttime enuresis (Nevéus 2011).

Epidemiologically, enuresis is more common in boys than in girls and is more common in younger children. According to DSM-5, enuresis is present in 7% of boys and 3% of girls at age 5 years. Other studies have cited prevalence rates of 15% for boys and 12% for girls, but rates are consistently higher in boys at all ages. Prevalence is inversely proportional with age for both sexes, decreasing by approximately 15% per year (Forsythe and Red-

mond 1974; Klackenberg 1981), with remission occurring by age 18 in the large majority of cases.

Enuresis often appears to be heritable, based on multiple studies. One such study showed the familial risk of enuresis to be 2.6 times greater in siblings of children with enuresis than in siblings of children who do not have enuresis (Hyde et al. 2008). If a child's father was enuretic after age 4 years, the risk of that child having enuresis was 7.1 times greater (Järvelin et al. 1988). Linkage analyses in families with numerous members with enuretic disorders show possible chromosomal locations, including 4p16.1, 12q, 13q, and 22q11 (Wang et al. 2007).

An important and clinically often underestimated aspect of elimination disorders is psychiatric comorbidity. For children with nocturnal enuresis, 20%–30% have symptoms that fulfill criteria for another DSM-IV (American Psychiatric Association 1994) psychiatric disorder (von Gontard et al. 2011). For children with daytime enuresis, 20%–40% have symptoms that meet DSM-IV criteria for other psychiatric disorders. The most common comorbid diagnosis for children with enuresis is attention-deficit/hyperactivity disorder (ADHD); in a clinic setting, the comorbidity rate was 28.3% (Baeyens et al. 2006). One of the clinically relevant factors with this comorbidity is that compared with controls who do not have ADHD, children with ADHD are often more difficult to treat, are less adherent, and have worse outcome with standard enuresis treatments (Crimmins et al. 2003). In children with daytime urinary incontinence, psychiatric comorbidity is more complicated than in children with nocturnal enuresis; the former have higher levels of deviant behavior (von Gontard et al. 1999) and more widespread psychiatric issues, including ADHD (24.8%), conduct problems (11.8%), separation anxiety (11.4%), and oppositional behavior (10.9%) (Baeyens et al. 2007). Subclinical symptoms are often also present, given the social pressures of continence. Children note reduced self-esteem and lower quality of life while incontinent, but these symptoms apparently resolve when continence is achieved (von Gontard and Nevéus 2006).

Given the high prevalence of comorbidities, all practitioners would be prudent to use a screening questionnaire to assess for psychiatric symptomatology and to then treat and/or refer as necessary. Questionnaires recommended by von Gontard et al. (2011) include the Short Screening Instrument for Psychological Problems in Enuresis for screening. This questionnaire asks yes/no questions about seven emotional problems related to enuresis (e.g., "Does your child sometimes have the feeling that others are reacting negatively?" and "Does your child sometimes feel worthless or less confident?") and asks six yes/no questions that screen for ADHD. If necessary, the Child Behavior Checklist can be used for a more in-depth psychiatric profile.

Evaluation of Enuresis

Given the complicated anatomical and neurochemical bladder and bowel physiology, a systematic evaluation process is important for appropriate diagnosis and medical decision making for children with enuresis. The major international pediatric urology and nephrology societies have agreed on consensus guidelines for the management of enuresis (Vande Walle et al. 2012).

The two major categories of pediatric urinary incontinence are nocturnal enuresis and daytime urinary incontinence. The first basic question for all patients and families presenting with enuresis is

intended to determine whether the child has daytime and/or nighttime incontinence. Daytime urinary incontinence may require urological referral and should be treated prior to nighttime enuresis. *Daytime urinary incontinence* is defined as a wetting accident at least once every 2 weeks. It is caused by varying abnormalities of bladder function, including overactive bladder, voiding postponement and underactive bladder, dysfunctional voiding, and other conditions such as giggle incontinence and primary bladder neck dysfunction. Monosymptomatic *nocturnal enuresis* is defined as enuresis with no other lower urinary tract symptoms or history of bladder dysfunction and accounts for 80% of cases of enuresis in children. Children with nonmonosymptomatic nocturnal enuresis have lower urinary tract symptoms including pain, hesitancy, urgency, straining, and increased or decreased frequency.

Overactive bladder involves abnormal detrusor contractions during filling. Some symptoms that suggest overactive bladder include drops of urine in the underpants before and after voiding, intermittent or continuous leakage every day, any daytime incontinence past age 3.5 years, and voiding more than eight times per day. Voiding postponement occurs when children chronically avoid urination, resulting in a low frequency of voiding; this behavior eventually leads to weak detrusor contraction and an underactive bladder. Dysfunctional voiding occurs when the detrusor muscle contracts against a closed urinary sphincter. Dysfunctional voiding can be caused by a neurological lesion, but can also be due to non-neurogenic causes. Symptoms suggestive of dysfunctional voiding include voiding fewer than three times per day, holding maneuvers (Vincent's curtsy—pressing heel into perineum, leg crossing, and standing on tiptoes), interrupted urinary stream, or voids that occur one right after another. If significant overactive bladder or dysfunctional bladder symptoms are present, they should be treated initially and may require referral.

Initial screening also involves questioning about current urinary tract infections causing incontinence, because such infections must be treated with antibiotics. Urinalysis is also important to evaluate for urinary tract infection, diabetes mellitus, or other abnormalities of urine sediment. Sleep pattern and sleep hygiene assessment may be useful. Practitioners must also assess whether constipation is present; if so, this must be vigorously treated as the initial intervention, because urinary incontinence may resolve with effective bowel regulation alone (Loening-Baucke 1997). Lastly, comorbid psychiatric symptoms, family stressors, or other adverse life events should be assessed, because these can indicate greater treatment difficulty for these children.

Management of Enuresis

If daytime incontinence is diagnosed, initial treatment is a strict bowel and bladder program. The bowel program will be discussed in the encopresis section later in this chapter. A bladder program includes education, fluid restriction, and timed emptying of the bladder—that is, voiding during daytime waking hours by the clock every 1.5 or 2 hours (Nunes et al. 2010). If behavioral modification does not improve daytime incontinence, pharmacology is used. In the past, anticholinergic agents were used to treat overactive bladder or daytime incontinence; however, more recent data suggest that these medications may overdistend an already distended bladder and then aggravate constipation, which is a precipitat-

ing factor in urinary incontinence (Reiner 2010). Overactive bladder is often a result of detrusor contractions against a closed sphincter, causing increased voiding pressures, themselves sometimes leading to bladder overdistension or even vesicoureteral reflux. Therefore, newer medications, discussed later in this subsection, are focused on treating these specific causes.

Treatment approaches might include botulinum toxin injections into the detrusor muscle in children with neuropathic bladders to induce muscle relaxation of some duration. In placebo-controlled trials in adults, botulinum toxin has been shown to effectively treat neurogenic detrusor overactivity (Herschorn et al. 2011; Rovner et al. 2011) and improve quality of life (Sahai et al. 2009). Multiple pilot studies and open-label trials have demonstrated the promise of this agent in controlling otherwise treatment-refractory symptoms in youths with spina bifida (Deshpande et al. 2010), meningomyelocoele (Kajbafzadeh et al. 2006) or neuropathic bladder (Neel et al. 2007; Safari et al. 2010). Biofeedback can be used in some difficult cases to teach the child to consciously relax the sphincter. Dilation of the urethra that tears the external sphincter muscle, commonly performed prior to about 30 years ago, is frowned upon in such cases, whereas spinal cord/peripheral nerve direct stimulation is useful in very select cases (Franco 2007). These treatments highlight the fact that overactive bladder or daytime incontinence likely needs to be treated by urological specialists.

Treatment for nighttime enuresis can be either behavioral or pharmacological. Two of the most common treatments for nighttime enuresis are bedtime alarms and desmopressin. To optimize benefit and compliance with these treatments, it is important to choose the most appropriate method for the individual patient and family.

Bedtime alarms are a first-line behavioral approach to nighttime wetting. When wetness activates a sensor, an auditory alarm is triggered that wakes the child and indicates the need to void. This is a difficult, sleep-altering, time-consuming program that affects the child, parent, and possibly the entire household, because deep-sleeping children might not wake but parents probably will. Treatment should be continued for 2–3 months or until the child is dry for 14 consecutive nights. Although this treatment is difficult, the long-term cure rate is approximately 50% (Glazener et al. 2005). Compliance is often low; therefore, early education and discussion are necessary to determine whether a family may be likely to succeed with this treatment modality. Compliance can be improved if the following conditions exist: 1) a parent is available to sleep in the child's room to make sure the child awakens and gets up to use the bathroom when the alarm goes off; 2) the family is able and willing to adhere to treatment 7 days a week; 3) the provider can follow up with the family by phone within 2 weeks of initiation to provide technical support and encouragement; and 4) treatment continues until there are 14 consecutive dry nights. If no improvement occurs after 6–8 weeks, treatment should be discontinued (Nevéus 2011).

Other nonpharmacological treatments have been studied with varying results. Psychoeducation, including pelvic floor control, voided volume, uroflow (i.e., efficiency of bladder emptying as measured by amount of urine and strength of flow), incontinence, and stool habits, led to a positive effect in 92% of the children versus the waiting-list controls, with 42% becoming completely dry after 6 months (Hoebeke et al. 2011). A Cochrane review

(Huang et al. 2011) for complementary interventions for nocturnal enuresis showed overall poor quality of trials and limited evidence for hypnotherapy, acupuncture, medicinal herbs, and chiropractic manipulations. However, Bower and Diao (2010) note that when acupuncture is evaluated by Western-trained physicians with limited knowledge of acupuncture, results are skewed toward the negative, and the authors argue that according to their findings in Chinese-language literature, acupuncture had higher response rates than the bedtime alarm.

Desmopressin is a synthetic analog of arginine vasopressin (also termed *antidiuretic hormone*), which has a short half-life and therefore reduces the volume of urine overnight. Desmopressin is available in tablet, nasal spray, or melt formulations. The nasal formulation is used sparingly because it has a black box warning of seizure risk, likely due to nonuniform mixing (shaking) and thus uneven dosing. The melt formulation is often preferred by children under age 12 (Lottmann et al. 2007). Dosing should start at 0.1 or 0.2 mg and increase by 0.2 mg every few days based on response. The maximum recommended dose is 0.6 mg in children and 0.8 mg in adolescents (Glazener and Evans 2000). Medication is to be taken 1 hour before last void of the evening, and fluid intake should be reduced for 8 hours to encourage appropriate concentrations. If patients do not comply with fluid restriction, the chance of hyponatremia and seizures may be increased, especially in younger and smaller children. The most common adverse effects include headaches or hypertension. It is important to note that unlike behavioral approaches, desmopressin does not affect sleep architecture, which may make it a preferred treatment option in some cases (Rahm et al. 2010). The recommended length of an initial desmopressin trial should be 2–6 weeks to assess efficacy. If there is improvement, treatment should continue every night for 3 months. At this point, treatment breaks can ascertain if continued treatment is necessary.

A prospective randomized crossover study (Kwak et al. 2010) confirms equal efficacy in a 12-week treatment using desmopressin or an alarm. Successful response was found in 77.8% of the desmopressin group and 82% of the alarm group. After crossover there was no statistical difference in either group; therefore, there is no statistical difference in the order of treatment. However, there was a higher relapse rate after desmopressin was discontinued. Alarm systems are not without their own drawbacks, as demonstrated in a study comparing long-term desmopressin and alarm (Evans et al. 2011) in which 32% of patients using the alarm withdrew versus 7% of desmopressin patients.

A second-line pharmacological treatment for monosymptomatic nighttime enuresis is imipramine, which has shown efficacy in double-blind placebo-controlled studies because it has multiple useful properties, including anticholinergic as well as urine-concentrating effects. Dosing is started at 0.5 mg/kg 1 hour prior to bedtime, and the dose is increased every 4–5 days by 0.5–1.0 mg/kg to a maximum of 2.5 mg/kg. Serum levels should be checked within 1 week of dose increases (Reiner 2010). Care should be taken to complete a cardiovascular history and obtain an electrocardiogram (ECG) prior to treatment, because cardiotoxicity is a side effect of imipramine. Given the lethality in overdose, monitoring for suicidality and locking up medications are important. Tolterodine, a more selective muscarinic receptor antagonist, can also be used for its anticholinergic effect at a starting dose of 2 mg 1 hour prior to bedtime; re-

sponse can be seen within 1–2 months (Nevéus et al. 2010).

If the symptoms are determined to be due solely to monosymptomatic enuresis (i.e., nighttime wetting with no evidence of overactive bladder or dysfunctional bladder), the consensus for optimal evaluation is the completion of urinary pattern diaries (von Gontard and Nevéus 2006). These diaries include measurement of fluid intake, as well as volume of daytime and nighttime urine voids as measured by diaper weight changes from placement to removal. Calculating the values of nocturnal urine production, expected urine bladder capacity, and maximum voided volume throughout the day can help differentiate between the subtypes of monosymptomatic enuresis, including nocturnal polyuria and smaller than expected bladder capacity. Subtyping enuresis helps drive appropriate treatment. For example, patients with nocturia (i.e., excessive sleep-related urine production) will be more sensitive to the use of desmopressin because this treatment temporarily reduces the volume of urine after dosing, thereby decreasing absolute sleep-time urine production and reducing chances for detrusor contractions during sleep periods. Alternatively, children with a smaller than expected bladder capacity will likely be resistant to desmopressin and more sensitive to sleep-time alarm systems. However, these calculations and measurements are also likely outside the scope of a psychiatrist's practice; therefore, consensus guidelines recommend discussing the two first-line treatments, desmopressin and bedtime alarms, with families and working together to determine which treatment to try initially.

Encopresis

The term *encopresis* is derived from the Greek word *kopros*, meaning "dung." According to DSM-5, *encopresis* (functional incontinence) is the involuntary or intentional passage of feces into inappropriate places that occurs at least once per month for at least 3 months (Box 7–2). The passage of feces is not attributable to the physiological effects of a substance, such as laxatives, or another medical condition. Chronological or developmental age must be at least 4 years. DSM-5 includes two specifiers: 1) with constipation and overflow incontinence and 2) without constipation and overflow incontinence.

Box 7–2. DSM-5 Criteria for Encopresis

307.7 (F98.1)

A. Repeated passage of feces into inappropriate places (e.g., clothing, floor), whether involuntary or intentional.
B. At least one such event occurs each month for at least 3 months.
C. Chronological age is at least 4 years (or equivalent developmental level).
D. The behavior is not attributable to the physiological effects of a substance (e.g., laxatives) or another medical condition except through a mechanism involving constipation.

Specify whether:

With constipation and overflow incontinence: There is evidence of constipation on physical examination or by history.

Without constipation and overflow incontinence: There is no evidence of constipation on physical examination or by history.

There is some disagreement between disciplines on the explanatory utility of the DSM diagnostic criteria (von Gontard 2013), which do not clearly delineate specific symptom frequency and severity. Gastroenterologists have developed the Rome III diagnostic criteria for functional constipation, which complement the DSM criteria but are more descriptive (Rasquin et al. 2006). Diagnosis using the Rome III criteria requires two or more of the following symptoms occurring at least once a week in a child age 4 (or developmental equivalent) for at least 2 months:

1. Two or fewer defecations in the toilet per week
2. At least one episode of fecal incontinence per week
3. History of retentive posturing or excessive volitional stool retention
4. History of hard or painful bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large-diameter stools that may obstruct toilet

In addition, symptoms are not better explained by or criteria are not met for irritable bowel syndrome.

Frequently, when a child is constipated and has retained fecal mass, liquid fecal matter will leak around this mass and is termed *overflow incontinence.* This leakage can lead to stained underpants, foul odor, and social stigmatization, as well as an incorrect diagnosis of diarrhea. Overflow incontinence cannot exist without constipation, because there is no retained stool blocking the passage of liquid fecal matter. Therefore, the second DSM-5 specifier, "without constipation and overflow incontinence," means that neither is present. To avoid confusion, for the remainder of this chapter, we use the terms *retentive incontinence* (with constipation and overflow incontinence) and *nonretentive incontinence* (neither constipation nor overflow incontinence).

Fecal incontinence is estimated to affect 0.8%–4.1% of children in Western societies (van der Wal et al. 2005) and 0.8%–7.8% globally (Rajindrajith et al. 2013). Males are 3–6 times more likely to have fecal incontinence than females. Retentive incontinence is 4.5 times more common than nonretentive incontinence. Risk factors for fecal incontinence include lower socioeconomic status and inadequate toilet facilities (van der Wal et al. 2005).

Functional constipation is often triggered by an event that causes fear of defecation, such as passage of a painful stool, fear of the toilet, and sometimes other aspects of anxiety or adjustment problems. This leads to withholding behaviors, including posturing (contracting gluteal muscles, stiffening legs, and tightening anal sphincter). Retention of stool distends the colon, can inhibit motor activities, and leads to slower colonic transit times. The longer fecal transit times are, the more water is absorbed, leading to more constipation and even harder stools and painful bowel movements, while perpetuating the cycle of voluntary withholding. This can lead to retentive incontinence as described above when overflow incontinence is present.

An example of nonretentive encopresis is a partial or full stool in the underwear with little evidence of pathological changes and no evidence of constipation. Causes of this encopresis are less clearly delineated. Some children with nonretentive incontinence have a history of severe behavioral problems, neglect, and abuse. It is especially important with nonretentive incontinence to rule out or-

ganic causes, including Hirschsprung disease, anatomical anal problems, history of bowel removal, inflammatory bowel disease, long-standing diabetes, or spinal cord damage (Har and Croffie 2010).

Evaluation of Encopresis

Evaluation of encopresis (Rajindrajith et al. 2013) should include a physical examination of the abdomen to assess for a fecal mass, especially in the left lower quadrant of the abdomen; examination of the spine to look for hair tufts or dimples; and anal observation to look for scarring or anatomical abnormalities, stool leakage, or mucus seepage. If laxative abuse is suspected, a basic metabolic panel is suggested to rule out magnesium abnormalities. An abdominal plain radiograph can show the amount of fecal load; however, a systematic review (Berger et al. 2012) found a wide range of sensitivity and specificity in terms of the specific film reviewer and suggested that this radiography often does not change diagnosis. Although imaging is sometimes useful to convince the parents that the problem is real, based on this review, abdominal plain radiography is not currently recommended for diagnostic purposes. Colonic transit studies have been used to differentiate between nonretentive and retentive incontinence; the latter had delayed transit time and the former had normal transit time in 88% of the studies (Benninga et al. 1994). In anorectal manometry, a tube is inserted into the rectum and a balloon is gently distended. Various tests can be done to measure when the patient senses the balloon, which measures sensation, and the patient can voluntarily contract his or her muscles as if having a bowel movement, enabling measures of sphincter tone and strength. Therefore, this test assesses the status of external and internal sphincter function and can rule out Hirschsprung disease if sensation and tone are intact. Anal endosonography visualizes the sphincters by inserting an ultrasound probe in the rectum. This test can show significant thickening of the internal anal sphincter in retentive incontinence, but is also used to diagnose fissures or other anatomical abnormalities that affect sphincter functionality (Keshtgar et al. 2004).

Children with fecal incontinence are more likely to have comorbid psychiatric symptoms. They have higher rates of oppositional defiant disorder (11.9%), ADHD (9.2%), separation anxiety (4.3%), specific phobias (4.3%), and generalized anxiety (3.4%). They also have subclinical symptoms, including lower self-esteem and lower social functioning, as well as feeling less able to control the positive aspects of their lives (von Gontard and Nevéus 2006). Children with combined enuresis and encopresis have even higher rates of psychiatric illness.

Management of Encopresis

Treatment of retentive incontinence is focused on treating the underlying constipation. Initially, it was believed that constipation leads to anatomical changes in the urinary tract system, causing enuresis. However, with further study, rectal distension has been found to decrease amplitude and shorten the duration of bladder contraction by neural feedback through the myenteric plexus. With increased intra-abdominal pressure due to high stool load, there is lowering of the pelvic floor, which makes it more difficult for the external sphincter to relax, as well

as strengthening of the detrusor muscle, decreasing detrusor compliance, flexibility, and filling of the bladder (Franco 2011a). Therefore, evacuation of the bowel is central to the treatment of both elimination disorders.

Theoretically, the purpose of disimpaction is to reset the bowel system with the hopes of restoring normal storage and evacuation function. Disimpaction is achieved by oral solution or rectal enemas. Two preferred oral solutions are mineral oil or polyethylene glycol (PEG; Tolia et al. 1993; Youssef et al. 2002), which result in clearance of impacted stool in 55%–100% of cases in a mean of 5.7 days. Both solutions are safe and have minor adverse effects, such as diarrhea and abdominal pain. Other options for oral disimpaction include lactulose or magnesium salts; however, there are limited controlled trials supporting their use (Constipation Guideline Committee of the North American Society for Pediatric Gastroenterology 2006). For rectal enemas, mineral oil, sodium phosphate, or saline can be used with good efficacy. Although some physicians believe enemas are overly invasive, both oral and enema treatments are relatively well tolerated in the child population (Bekkali et al. 2009). It is important to avoid enema-delivered substances containing milk and molasses or soapsuds, because they can cause significant hemodynamic compromise and colitis, respectively (Sheibani and Gerson 2008; Walker et al. 2003).

Once disimpaction is completed, maintenance therapy is initiated. An important component of maintenance treatment is behavioral change in dietary intake and toileting routine. Parental education must focus on adequate hydration with fluids, avoidance of constipating foods (chocolate, caffeine, milk products), and utilizing the gastrocolic reflex, ensuring that the child sits on the toilet immediately after breakfast and dinner for 10 minutes daily (Reiner 2010). Behavioral charts are important to document progress and provide positive reinforcement of the child's improved toileting habits by way of collecting points toward predetermined rewards.

Pharmacological and other oral interventions include increased daily fiber intake with soluble or insoluble fiber as tolerated (suggested 25–30 g/day), stool softeners, and laxatives such as senna leaf products. Soluble fiber dissolves in water, forms a gel-like substance, and swells; this slows digestion and can lower low-density lipoprotein (LDL) and blood glucose levels as a result of this slowing transit time. Insoluble products do not dissolve in water and act more as laxatives, adding bulk and decreasing constipation. A combination of each type of fiber is important, and both are available as dietary products or in supplements. Insoluble fiber products are typically mixed with liquid and have variable compliance due to taste and texture (Reiner 2010) but are now available in capsules. Soluble fiber is found in gummy bears, fiber products, and fiber cereals, or is available as a tasteless powder to dissolve in liquid. Dietary fiber also is found in the indigestible portion of fruits and vegetables. Increasing intake of natural foods that are high in fiber and water content, such as fresh fruits and vegetables, has positive health consequences that go beyond promoting bowel regularity, although compliance in children can be problematic.

Stool softeners include oral mineral oil or docusate sodium. The effectiveness of mineral oil treatment of encopresis with constipation has not been verified by placebo-controlled studies, but in noncontrolled clinical studies, response rates have been found to be equal to those for

PEG (Rafati et al. 2011). To make the taste more tolerable, one suggestion is to emulsify mineral oil with ice cream and milk (Reiner 2010). Side effects include possible anal leakage or potential aspiration that can lead to lipoid pneumonia (Zanetti et al. 2007). Docusate sodium has not been studied in pediatric populations and therefore cannot be recommended at this time. Laxatives stimulate water retention in the colon, thereby maintaining stool's softness and ease of passage. Laxatives may need to be used twice per week for stooling regularity.

The most widely studied and used product is polyethylene glycol, properly termed a *stool softener.* It comes in a variety of formulations, both with and without electrolytes. The varying options cause difficulty in obtaining clear evidence-based recommendations regarding which formulation is best. However, PEG with and without electrolytes have both been shown to be superior to placebo (Thomson et al. 2007) and potentially superior to docusate (Gordon et al. 2012). PEG can be used daily. Children often require intermittent or regular treatment for years with maintenance therapy of fiber products, PEG, and occasional laxatives (Reiner 2010).

Potential medications for encopresis include serotonin agents, opioid antagonists, and chloride channel activators. One of the most promising medications may be prucalopride, a specific serotonin (5-HT) receptor agonist. It has proven efficacious in studies of adults with constipation, resulting in reduced colonic transit times, softer stools, and decreased straining (Tack and Corsetti 2012). Prucalopride has limited side effects and results in no ECG changes, as occurs with other serotonin agents. The only open-label pilot study in children is by Winter et al. (2009). This study demonstrated that 58% of subjects were rated very much improved by parents and investigators. Mild adverse effects were noted by 70% of the subjects; the most common were headache, abdominal pain, and respiratory tract infections. No serious side effects or cardiotoxicity was reported. Prucalopride is currently being studied as a treatment for pediatric encopresis related to constipation in a multicenter, phase III randomized controlled trial.

A biofeedback procedure that has been used involves anorectal manometry: A catheter with a balloon is inserted in the rectum. The balloon is inflated while the child is gradually trained to relax the external sphincter while attempting to push out the mass (Har and Croffie 2010).

In extreme cases of constipation, a surgical method called the *Malone antegrade continence enema,* or ACE procedure, may be used. It involves creating a stoma with the appendix; the tip is excised and surgically brought out to the abdominal wall. When needed, a catheter is inserted to wash out the colon with salt-water enemas.

No clearly effective pharmacological or biological treatment for nonretentive incontinence has emerged from clinical studies. In fact, treatment with laxative agents is contraindicated because they may exacerbate the problem. Instead, clinical management should focus on behavioral interventions that include clear consequences for incontinence, especially soiling outside the underpants, combined with careful diagnosis and treatment of comorbid psychiatric disorders (van Ginkel et al. 2000).

Conclusion

Given the complicated interplay of the urinary and bowel systems, both enuresis and encopresis are difficult to diagnose and therefore to treat. Eliciting clear

histories can help guide management. For enuresis, daytime incontinence may require referral to a specialist in pediatric urology, but nighttime incontinence may respond to desmopressin or nighttime alarm. Encopresis with constipation often responds to disimpaction followed by maintenance therapy and behavioral changes. Encopresis without constipation does not respond well to current treatment modalities.

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PART II

Schizophrenia Spectrum and Other Psychotic Disorders

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The diagnosis and treatment of psychotic disorders with DSM-5 are virtually similar to approaches in years past. DSM-5 brings only modest change to our conceptualization of psychotic illness, even though the description of schizophrenia itself with respect to its psychopathology is expanded in detail. The schizophrenia spectrum concept now includes, along with schizophrenia itself, schizotypal personality disorder (also still classified under personality disorders), delusional disorder, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, and other specified (including attenuated psychosis disorder) and unspecified schizophrenia spectrum and other psychotic disorder. It is specified that the schizophrenia diagnosis must be based on at least two symptoms of psychosis. Hence, the criteria no longer allow a single delusion alone, however bizarre, to indicate schizophrenia.

Traditional descriptors of schizophrenia subtypes (e.g., paranoid, disorganized, and catatonic) were dropped from DSM-5 because of their lack of relevance. Domain ratings were added descriptively, albeit not used for diagnosis. There are nine proposed psychosis domains in field trials, and the eventual number of domains will depend on their reliability. The diagnosis of schizoaffective disorder is more stringently specified to require greater overlap of mood symptoms throughout the lifetime of psychosis; specifically, mood symptoms must be comorbid with psychosis at least 50% of the time. Finally, attenuated psychosis syndrome is not a discrete disorder in DSM-5, since it has not yet been established in clinical practice, despite its specified criteria and manifestations. It is classified as other specified schizophrenia spectrum and other psychotic disorder.

Overall, these recommended changes adopted in DSM-5, though modest, were

those determined necessary to make the diagnosis of schizophrenia more valid, reliable, and clinically useful.

Treatments of psychotic disorders are detailed in Part II of this volume. It is most striking that recommended treatments are not only pharmacological, as described in detail by Philip Janicak in Chapter 11 ("Pharmacological Treatment of Psychosis"), but include cognitive and psychosocial treatments as well, as described by Matcheri Keshavan and Shaun Eack in Chapter 10 ("Psychosocial Treatments for Chronic Psychosis"). The efficacy of cognitive treatments carried out in the context of optimal antipsychotic drug management has been surprisingly high and raises our expectations of plasticity-induced, use-dependent approaches for altering disease manifestations. As schizophrenia treatments mature, remediation efficacy will require that the full treatment of individuals with psychotic disorders include cognitive as well as pharmacological approaches. In addition, treatments have become specialized to disease stage, with S. Charles Schulz and colleagues describing, in Chapter 8 ("Early-Stage Schizophrenia"), treatment in very early schizophrenia. It is widely assumed, even though unproven, that disease manifestations are more plastic in their early phase and that successful treatment will alter disease course, an assumption that is true in other diseases, such as diabetes and hypertension. The schizophrenia spectrum disorders have diverse and highly variable manifestations that can change over the disease course, requiring treatment considerations that are personal and targeted.

Psychiatrists have always designated psychosis treatments by symptom domains (e.g., antipsychotic treatments directed toward psychosis) rather than by DSM-specified diagnoses. Psychosis is the most critical treatment-specifying domain for schizophrenia and supports many different and similarly active antipsychotic medications. Schizoaffective disorders, manifesting both as psychosis and as concurrent mood symptoms, involve treating two domains with both antipsychotic and mood-stabilizing or antidepressant medications, as needed. Specifically, the treatment of schizoaffective disorders should include a focus on psychosis with an antipsychotic medication and a focus on the affective symptoms with either a mood stabilizer or an antidepressant. To some degree, the second-generation antipsychotics, many of which are indicated both for psychosis and for depression, can be considered for both symptom sets. For negative symptoms and for cognitive dysfunction, despite a high level of interest and investigation, treatments do not yet exist. Once such treatments become available, however, they will be used in combination, as are antipsychotics and antidepressants as cotreatments for schizoaffective disorder.

The single most limiting feature in psychosis treatment is the lack of any reliable known biomarkers of illness that can be used for classification, treatment prediction, or disease management, let alone as a target for drug development. The illness classifications in psychotic illness are based on phenomenology and not, as of yet, on biological manifestations or phenotypic expression. Carol Tamminga and Elena Ivleva, in Chapter 9 ("Toward a Dimensional Understanding of Psychosis and Its Treatment"), look to the future, when biological criteria will specify categorization in psychosis and the defining criteria being biomarkers. One could anticipate that these biomarkers will then be used as targets for novel treatment development. All of our medications in psychiatry have been serendipitously identified. Now, as disease-defining biology becomes a reality and a

generation of molecular pathophysiology research appears promising, progress in defining the actual diseases included within the psychosis domain is likely to become a reality. Modern neuroscience and genetics will generate the cellular and molecular targets for these advances, from areas where advances are widely anticipated, given the broad state of discovery in neuroscience, genetics, and clinical-translational research. Understanding of the genetics of serious mental illnesses has advanced quickly over recent years, as analyses of large sets of DNA from patients have been carried out, including the genotyping of more than 25,000 samples from psychotic probands contrasted with samples from more than 30,000 control subjects from giant international consortia. Lately, these studies have generated more than 60 "hits" for psychosis risk genes from genome-wide association studies and copy number variation analyses. The hits are clearly manifest across the genome nonrandomly and are observed to cluster within groups of genes that code for synaptic proteins, the *N*-methyl-D-aspartate receptor and synaptic plasticity, ion channels, neuronal adhesion molecules, and mitochondrial RNAs, among others. Moreover, there are overlapping risk genes for phenomenologically distinct disease clusters, with one study identifying at least five common risk genes for schizophrenia, bipolar disorder, depression, ADHD, and autism, suggesting that disease genetics are pleiomorphic across DSM diagnoses. Our understanding of the biological basis of functional brain diseases is likely to advance categorically over the next few decades. The time is in sight when biology will emerge for serious mental illness and molecular targets will generate specific treatments for diseases that at present we know only as syndromes.

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CHAPTER 8

Early-Stage Schizophrenia

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Early stages of schizophrenia have not always been conceptualized as being on the continuum with chronic stages of the disease. In fact, historically, treatment was withheld until symptom presentation had solidified into systematically defined schizophrenia. During the 1980s, researchers and clinicians began to recognize that delay in treatment, including the initiation of antipsychotic medications, could lead to poor social, cognitive, and functional outcomes (Johnstone et al. 1986). This revelation prompted further research into the detrimental impact of longer duration of untreated psychosis—that is, the time from onset of schizophrenia symptoms to initiation of medication treatment. These studies led to substantial examination of the assessment and management of schizophrenia in young people and the development of revised clinical programs worldwide (Perkins et al. 2005).

Interest in emerging psychosis has also enhanced and motivated research aimed at investigating the pathophysiology of first-episode psychosis. Brain imaging has been a major tool in acquiring further knowledge of schizophrenia and other severe psychiatric illnesses. Researchers have also assessed first-episode patients. In those studies, structural differences were found in adolescent patients compared with nonpsychotic patients and control subjects (Schulz et al. 1983). Further studies confirmed these structural differences with magnetic resonance imaging (MRI) (Degreef et al. 1992; Friedman et al. 1999). The findings from these imaging studies were complemented by findings of decreased neuropsychological testing scores in adolescents (Kenny et al. 1997) and in young adults (Addington et al. 2005). This corroboration has been essential in underscoring the importance of recognizing the pathophysiological continuity in schizophrenia across time.

As examination of the early stages of schizophrenia heightened, a number of

investigators began to focus on the critical prodromal syndrome of the illness in order to characterize the symptoms that could lead to this early recognition. The prodrome programs have developed useful assessment tools (Cannon et al. 2008) and examined a number of useful treatment approaches, ranging from cognitive therapy to administration of medications.

Programs around the world not only have begun treating younger people but also have worked to make communities aware of early symptoms of schizophrenia. Interventions started closer to illness onset have been seen to reduce suicidality, and beginning treatment earlier in young people has led to less severe symptoms and improved insight.

In this chapter, we address approaches to identifying, medically investigating, and treating early-stage schizophrenia, with a focus on treatment of prodrome symptoms and first-episode psychosis in adolescents and young adults. We critically review medication management. We also focus on the important psychosocial aspects of treatment, including family involvement, substance abuse management, cognitive remediation, and other therapy modalities. Finally, we address barriers to symptomatic improvement and next steps in treatment.

First-Episode Psychosis and Prodrome Workup

First-episode psychotic symptoms, as well as prodrome symptoms, warrant a systematic medical workup to exclude medical causes of psychosis. A comprehensive laboratory and imaging assessment strategy has been compiled by Massachusetts General Hospital Schizophrenia Program in collaboration with Harvard Medical School (Freudenreich et al. 2009; see Table 8–1). The diagnosis of schizophrenia requires an absence of a medical condition that could account for the observed and experienced psychopathological signs and symptoms. A sample screening battery was proposed that could be included in a thorough examination. Completing such an examination ensures that there is no delay in treatment of a medical illness, that schizophrenia is reliably diagnosed, and that the medical baseline (e.g., metabolic status) is established before beginning treatment.

The recommended battery includes screens for varieties of psychosis, as well as for typical and atypical presentations. For example, because drugs are common causes of psychosis, a urine toxicology screen is useful. Most common medical ailments rarely present with psychosis, but some occasionally do. For instance, an HIV seroconversion could present as acute psychosis. Additionally, some uncommon diseases, such as acute intermittent porphyria, can present classically with psychosis. Rarely diagnosed conditions, such as Tay-Sachs disease, Niemann-Pick disease, or Wilson disease, can also present with symptoms identical to those of schizophrenia.

These categories of illnesses and presentations were considered carefully when the proposed diagnostic workup provided in Table 8–1 was being developed. In a subset of 268 patients with first-episode psychosis, 9 (3%) were found to be suffering from an organic disease (Freudenreich et al. 2009). Of those 9 individuals, 3 were diagnosed with neurosyphilis, 2 with neurosarcoidosis, 1 with lung cancer, 1 with autoimmune multisystem disease, 1 with cerebral cysticercosis, and 1 with thyrotoxicosis.

In addition, because many offices and clinics are seeing patients who are possibly in the prodromal phase of schizophre-

TABLE 8–1. First-episode psychosis workup

Tier 1: All patients with new-onset psychosis
Complete blood count
Comprehensive metabolic panel
Thyroid-stimulating hormone and reflex to free thyroxine
Urinalysis
Urine screen for drugs of abuse
Urine pregnancy test for all women of childbearing age
Vitamin B_{12} levels
Red blood cell (RBC) folate
Fasting lipid panel
Fasting glucose levels
Electrocardiogram
Treponemal antibody enzyme immunoassay
Lyme titer
Erythrocyte sedimentation rate
Antinuclear antibody
Ceruloplasmin
HIV serology
Chest X ray (to aid in detection of sarcoidosis or other pulmonary disease)
Magnetic resonance imaging (MRI) of brain without contrast
Tier 2: Consider in patients with new-onset psychosis if indicated by presentation or history
Heavy metal screen
Urine for porphyrins
Additional viral serologies (hepatitis B virus, hepatitis C virus)
Other sexually transmitted disease screens
Testing for adrenoleukodystrophy and other inherited metabolic disorders
Testing for Huntington's disease
Screen for velocardiofacial syndrome (VCFS)/22q11 deletion
Testing for tuberous sclerosis
Testing for adult-onset Tay-Sachs disease
Testing for Niemann-Pick disease
Screening for paraneoplastic syndromes
Consideration of formal neuropsychiatric testing
Consideration of lumbar puncture if clinically warranted
Consideration of electroencephalography if clinically relevant

nia, White et al. (2006) have described the differential diagnosis, which includes psychiatric disorders such as posttraumatic stress disorder, affective disorders, and personality disorders, as well as medical illnesses that may lead to psychosis.

At-Risk Mental State (Prodrome)

Overview

It has been known for decades, from obtaining histories of early-stage patients with schizophrenia, that the onset of psychosis is frequently preceded by symptoms such as social withdrawal, difficulty in school, and suspiciousness. As interest in early intervention grew, identification and intervention strategies emerged (McGorry et al. 2002a). In many ways, the differing views of the lead-in to schizophrenia were solidified by Yung et al. (2006), who reviewed the background of antecedent symptoms. This work led to focusing on ultra-high-risk, which was a format for clinical studies.

Investigators interested in the prodromal phase of illness have used brain imaging to examine anatomical and functional arenas. Pantelis et al. (2003) performed MRI scans on a group of prodrome research subjects and noted structural differences from scans of normally developing individuals. Further imaging revealed a progression in structural changes for those prodrome patients who developed schizophrenia. Fusar-Poli et al. (2010) used positron emission tomography scans to examine dopamine activity in prodrome subjects and reported dysfunction in those young people who went on to develop schizophrenia.

Another area of interest is whether the cognitive issues seen in schizophrenia are evident during the prodromal phase. To explore this possibility, Seidman et al. (2010) examined prodrome patients and observed cognitive decline during this phase of illness. Notably, poor function was evident even in those with only a family history of psychosis. These findings from imaging and cognitive testing support the significance of addressing the prodromal phase of schizophrenia.

The prodromal period of schizophrenia occurs primarily in adolescents and young adults who present with attenuated positive psychotic symptoms, with brief limited intermittent psychotic symptoms (lasting less than 1 week and resolving spontaneously), or with schizotypal personality disorder. These individuals describe pulling back from social life and having difficulty in school. Individuals with a first-degree relative with a psychotic disorder who have experienced a significant decline in mental state or cognitive functioning over the previous year are also at significant risk (Cannon et al. 2008). An important study that is useful in identifying prodrome patients and devising a treatment plan is that of Olvet et al. (2013), who have investigated the prodrome and noted conversion to bipolar disorder or depression in some prodrome patients. Evaluation and follow-up are thus important parts of management of these young patients, especially for those in a pharmacological treatment plan.

Given the importance of early identification and treatment of psychotic illness, *attenuated psychosis syndrome* has been added in Section III, "Conditions for Further Study," of DSM-5 (American Psychiatric Association 2013) and is cited as an example of other specified schizophrenia spectrum and other psychotic disorder in Section II. Individuals with this syndrome have psychosis-like symptoms that are below the threshold for one of the primary psychotic disorders. Potential benefits of this addition to DSM-5 include earlier recognition and treat-

ment of youths at high risk and the potential to prevent transition to primary psychotic disorder or other severe mental illnesses.

Treatment

Young people early in the disease process require specialized interventions unique to their stage of illness. Agius et al. (2010) proposed a staging system to categorize appropriate diagnosis and treatment. They suggested that schizophrenia can be separated into prodromal, first-episode, and chronic stages, much like stages of other complex medical illnesses. Initial intervention during the prodromal stage can begin with the lowest risk and least invasive treatments; these include psychoeducation, stress reduction, and cognitive-behavioral therapy (CBT).

While these talking therapy treatments are applied, neuroprotective agents can also be considered as first-line intervention for those in the prodromal stage. A study evaluating the use of omega-3 fatty acids reported efficacy in reducing the transition rate to first-episode psychosis from the prodrome (Amminger et al. 2010). Omega-3 fatty acid treatment was also shown to improve positive and negative symptoms, as well as preserve global functioning. For adolescents and young adults in the prodromal phase of illness, the side effects were very low. Further confirmatory studies are under way.

The prodrome itself is a continuum, and if illness has progressed and if CBT and neuroprotective agents such as omega-3 fatty acids have proven ineffective, antipsychotic medications can be considered as a next step in treatment. In 2002, the PACE Intervention Trial used low-dose risperidone (1–2 mg/day) in combination with CBT. Subjects who were adherent to risperidone treatment had a significantly lower rate of transition to psychosis (McGorry et al. 2002b). In the PRIME study, in which olanzapine was tested, there was no statistical difference between olanzapine and placebo in conversion rates; however, there was an advantage for olanzapine regarding prodrome symptoms (Woods et al. 2003).

Of some controversy in the field was a comprehensive study by McGorry et al. (2013), in which CBT plus medication, CBT plus placebo, and supportive therapy plus placebo were compared. Of special interest were the similarly low conversion rates of about 11% for CBT plus medication and 10% for CBT alone. These findings will need to be followed as this field progresses.

Bechdolf et al. (2011) reported equal efficacy for treatment with low-dose aripiprazole (5–15 mg/day) or CBT. However, when participants were given a choice, most preferred CBT to medication management. This finding is similar to results from studies of other psychiatric illnesses. Consistent with first-episode psychosis recommendations, the lowest effective dose of antipsychotic medication is recommended in prodromal states at the appropriate stage or severity of illness. Agents with the lowest risk of metabolic side effects are considered first-line treatments. If clinical benefit is found with medication management, continuing pharmacological therapy is recommended for the next 6 months to 2 years.

Connecting to Young People

The risk of increased stigma in young people labeled as "at risk" of developing a psychotic disorder has been considered. In all ultra-high-risk or prodrome studies to date, the false-positive rate is 40%–50%, or even higher. It is widely agreed that young persons who are seeking help, es-

pecially those who also present with functional decline and distress, are in need of treatment. As stated in the preceding subsection, at the time the prodrome is recognized, cognitive decline is often already detectable. This deficit can account for observed decline in daily functioning. Prodrome patients are also at higher risk to self-harm or participate in other health-damaging behaviors (Yung et al. 2004).

Recently, 255 participants in the North American Prodrome Longitudinal Study were observed 2.5 years after being identified as meeting prodromal criteria. By 2.5-year follow-up, 35% had developed a psychotic illness; 24% had experienced remission of their attenuated symptoms; and 20% still had attenuated symptoms, although less severe than at baseline. (In addition, 21% had received an antipsychotic medication while in the prodromal stage, which precluded use of data from this group to describe natural course.) Unfortunately, only a minority of these young persons showed a complete remission of symptoms without treatment (Addington et al. 2011). Youths who "recovered spontaneously" were not in the majority; in fact, the study authors concluded that most of the youths in the "at-risk" group would most likely have benefited from initiation of psychiatric services when symptoms were identified to prevent progression into more serious illness.

Adolescent Onset of First-Episode Psychosis

Approximately one-third of people who develop schizophrenia have illness onset during adolescence (Loranger 1984). Individuals with early-onset schizophrenia have symptom onset between ages 13 and 18 years and have been observed to have greater symptom severity and poorer long-term outcomes (Krausz and Müller-Thomsen 1993). Underscoring the importance of early recognition of schizophrenia are imaging studies showing that structural brain changes are already present in adolescents (Schulz et al. 2005). Furthermore, National Institute of Mental Health (NIMH) intramural studies found that structural changes are progressive in the group with early-onset schizophrenia (Thompson et al. 2001). Despite the poor prognosis for youths with early-onset schizophrenia, early identification and treatment result in a more robust response to treatment. Therefore, treating youths in the earliest stages of the illness is constructive.

Therapeutic Interventions

Medication Management in Adolescents With Schizophrenia

Before we discuss specific medications for adolescents diagnosed with schizophrenia, it is important to mention the groundwork needed for this intervention. Both young patients and their family members should be engaged in a significant discussion of the rationale for the medications, their efficacy, and potential side effects. Adolescents and young adults are extremely sensitive to antipsychotic medication, so beginning at a low dose will aid in acceptance.

The first controlled trials of antipsychotic medications in teenagers did not emerge until the mid-1970s. In the first study (Pool et al. 1976), patients taking antipsychotics had greater improvement

than those given placebo. This study was followed by a comparison trial (Realmuto et al. 1984), which revealed challenges using traditional antipsychotic medications in teenagers due to movement disorder side effects. Controlled trials were not an area of attention in adolescent research until second-generation antipsychotics were developed. A large series of trials of second-generation antipsychotic medications (U.S. Food and Drug Administration registration trials) did show symptomatic advantages, which were somewhat offset by reported incidence of first-episode metabolic side effects and movement disorders. Table 8–2 outlines the monitoring protocol for these side effects.

TABLE 8–2. Monitoring protocol for metabolic adverse effects of atypical antipsychotics

Baseline	Family history	Height	Weight	BMI	Blood pressure	Fasting glucose	Fasting lipids	ECG
4 weeks	X	X	X	X	X	X	X	X
8 weeks			X	X				
12 weeks			X	X				
6 months			X	X		X	X	
Quarterly			X	X				
Annually						X	X	

Note. BMI=body mass index; ECG=electrocardiogram.

A summary of findings from studies of medication management in adolescents with first-episode psychosis is presented in Table 8–3.

Second-Generation Antipsychotic Medications

Risperidone. The first of the front-line atypical antipsychotic medications to be studied in adolescents was risperidone. In a double-blind, placebo-controlled trial comparing high-dose (4–6 mg/day) and low-dose (1–3 mg/day) strategies, both doses proved efficacious for the treatment of schizophrenia; however, patients receiving higher doses experienced a significant increase in adverse side effects—specifically, extrapyramidal symptoms and elevated prolactin (Haas et al. 2009b). These findings follow the observed trend that young people early in the disease process are typically more sensitive to side effects and that lower doses can lead to fewer side effects.

Olanzapine. Olanzapine was also tested in a double-blind, placebo-controlled trial with flexible dosing of olanzapine (2.5–20.0 mg/day), and a statistically significant difference between the medication and placebo was found (Kryzhanovskaya et al. 2009). However, in this study of adolescents with schizophrenia, those taking olanzapine experienced substantial weight gain (average gain of 4.3 kg). In addition, they had increases in triglyceride, uric acid, and prolactin levels and abnormal liver function (LFTs).

A study by Sikich et al. (2008) compared second-generation antipsychotic medications (including olanzapine) with

TABLE 8–3. First-episode psychosis antipsychotic studies in adolescents

Study	*N*	Age range, years	Drug and dosage, mean and range (mg/day)	Outcomes	Adverse effects[a]
Kumra et al. 1996	21	12.7–16.3	CLZ 178±149 HAL 16±8	CLZ treatment was statistically and clinically significant compared to treatment with HAL (BPRS-C, PANSS, CGI).	CLZ: Drowsiness and salivation 5 transitory neutropenia 2 seizure activity HAL: Insomnia 1 NMS
Sikich et al. 2004	50	8–19	HAL 2.0–5.0 OLZ 3.5–12.3 RIS 1.2–4.0	All the treatments were clinically and statistically effective. Between-group comparisons of the magnitude of improvement failed to detect statistical differences (BPRS-C).	EPS: 5% of those taking RIS, 33% of those taking HAL, and 0% of those taking olanzapine withdrew from the study due to EPS Sedation: OLZ (56%)>HAL (47%)>RIS (25%) PRL-related AE: Similar among groups Weight gain: Significant in all three

TABLE 8–3. First-episode psychosis antipsychotic studies in adolescents *(continued)*

Study	*N*	Age range, years	Drug and dosage, mean and range (mg/day)	Outcomes	Adverse effects[a]
Findling et al. 2008	302	13–17	ARP HD 30 ARP LD 10	Both ARP regimens resulted in statistically and clinically significant improvement compared with PL. Response rates were as follows: ARP HD 58%, ARP LD 54%, PL 36%. HD regimen resulted in an earlier improvement (PANSS; CGI-S, CGI-I)	EPS, somnolence, and tremor (HD>LD) Glucose and lipid metabolism–related AE: Akathisia: ARP=PL at 10-mg dose, but ARP>PL (significantly significant) at 30-mg dose
Kumra et al. 2008	39	10–18	CLZ 403.1 (50–700) OLZ 26.2 (10–30)	CLZ treatment resulted in statistically and clinically significant improvement compared with OLZ (SANS).	Weight gain: 13% gained >7% of baseline (3 CLZ, 2 OLZ) Glucose-lipid metabolism: Increase in fasting serum cholesterol, triglycerides, and glucose levels CLZ: 1 transitory neutropenia
Sikich et al. 2008	119				han for RIS or

TABLE 8–3. First-episode psychosis antipsychotic studies in adolescents *(continued)*

Study	*N*	Age range, years	Drug and dosage, mean and range (mg/day)	Outcomes	Adverse effects[a]
Haas et al. 2009a	257	13–17	RIS HD 1.5–6 RIS LD 0.15–0.6	HD regimen resulted in statistically and clinically significant improvement compared with LD regimen (PANSS, CGI-S).	EPS: HD (33%)>LD (10%) PRL level elevation: HD (97%)>LD (64%) PRL-related AE: 9 Weight gain: HD (82%; mean change: 3.2 kg)>LD (70%; mean change: 1.7 kg) Glucose and lipid metabolism-related AE: None
Haas et al. 2009b	160	13–17	RIS HD 5.3 (4–6) RIS LD 2.6 (1–3)	Both HD and LD regimens resulted in statistically and clinically significant improvement compared with PL; no difference was found between HD and LD at the endpoint (PANSS; CGI-S, CGI-I; CGAS).	EPS-related AE: HD (39%)>LD (33%)>PL (15%) PRL level elevation: HD>LD>PL PRL-related AE: None Weight gain: HD (mean change: 1.5 kg)>LD (mean change: 1.3 kg)>PL m: None

TABLE 8–3. First-episode psychosis antipsychotic studies in adolescents *(continued)*

Study	*N*	Age range, years	Drug and dosage, mean and range (mg/day)	Outcomes	Adverse effects[a]
Kryzhanovskaya et al. 2009	107	13–17	OLZ 11.1 (2.5–20)	OLZ treatment resulted in statistically and clinically significant improvement compared with PL (BPRS-C, PANSS, CGI-S).	EPS-related AE: no difference between groups PRL level elevation: OLZ (81%)>PL (16.7%) Weight gain: OLZ (45.8%; mean change: 4.3 kg)>PL (14.7%; mean change: 0.1 kg) Glucose and lipid metabolism–related AE: Fasting triglycerides and uric acid mean change OLZ>PL Mean change in ALT: OLZ>PL
Findling et al. 2012	222	13–17	QUE 400 QUE 800	Clinically significant improvement occurred in PANSS and CGI at both doses as compared with PL.	Somnolence, headache, weight gain (mean change: 1.8–2.2 kg), lipid elevation, and dizziness
Findling et al.	283				idal disorder, in-

molindone, a first-generation medication. The olanzapine arm was discontinued following the emergence of metabolic side-effects. Therefore, even though olanzapine was found to be efficacious in the treatment of schizophrenia in teenagers, the magnitude of metabolic side effects has led to the recommendation that the medicine not be used as a first-line intervention, although its use can be considered later in the treatment strategy.

Aripiprazole. Aripiprazole is a second-generation antipsychotic medication with partial dopamine agonist properties, which differ from the actions of other antipsychotic medications on dopamine receptors. When tested in adolescents in a double-blind, placebo-controlled trial (Findling et al. 2008), aripiprazole demonstrated a statistically significant advantage in the treatment of psychotic symptoms. Although higher dosages (30 mg/day) did result in earlier improvement, a dosage of 10 mg/day also resulted in clinical improvement. Even though fewer metabolic side effects have been reported for aripiprazole than other second-generation antipsychotics (Correll et al. 2009), complaints of akathisia were statistically significant (Findling et al. 2008).

Quetiapine. In a trial in adolescents with schizophrenia, quetiapine at dosages of 400 or 800 mg/day was compared with placebo in 220 patients. Symptoms of schizophrenia significantly improved, as measured by Positive and Negative Syndrome Scale (PANSS) total score change, during this 6-week trial. Mild to moderate weight gain and an increase in total cholesterol and triglycerides were also observed (Findling et al. 2012).

Ziprasidone. Ziprasidone was frequently used for adolescents with schizophrenia when first released because of a lower propensity for causing weight gain than other atypical antipsychotic medications. A published first-episode study showed significant symptom improvement response for ziprasidone. However, ziprasidone given to adolescents at dosages ranging from 80–160 mg/day did not result in improvement over placebo, according to Brief Psychiatric Rating Scale—Anchored (BPRS-A) scores (Elbe and Carandang 2008). Like aripiprazole, ziprasidone is favored in the early stages of illness because of its mild side-effect profile.

Clozapine for treatment-resistant early-onset schizophrenia. Although clozapine has been demonstrated to be effective in treatment-resistant schizophrenia, it is not frequently used in adolescents. In the first study of clozapine in teenagers, Kumra et al. (1996) demonstrated that in a group of teenagers with early-onset schizophrenia (onset before age 13), clozapine was superior to haloperidol in symptom reduction. The group also noted problems with electroencephalographic measures and white blood cell counts. In a later trial involving adolescents with treatment-refractory schizophrenia, Kumra et al. (2008) compared olanzapine at high dosages (up to 30 mg/day) with clozapine and noted that more of the adolescents responded to clozapine (66%) than to olanzapine (33%). With both treatments, patients gained a significant amount of weight. In an open-label follow-up, the adolescents who had originally been taking olanzapine were given clozapine, and 7 of those 10 individuals improved.

Comparison trials in adolescents. Individual registration studies can demonstrate the efficacy of a medication; however, direct comparisons are crucial in making treatment decisions. One comparison study randomly assigned adolescents to treatment with risperidone, olan-

zapine, or haloperidol (Sikich et al. 2004). All three medications were effective in treating psychotic symptoms; however, all three also demonstrated increased sensitivity to sedation and weight gain in adolescents as compared with similar studies in adults. Another study comparing risperidone, olanzapine, and molindone showed equal efficacy of second-generation and first-generation medications in treating schizophrenia in adolescents (Sikich et al. 2008). Molindone was associated with a higher risk of akathisia, whereas risperidone and especially olanzapine were associated with weight gain. For all adolescents taking olanzapine, the olanzapine was discontinued early because of weight gain.

Medication Management in Young Adults With First-Episode Psychosis

A number of the principles described in initiating medications in adolescents with the diagnosis of schizophrenia apply to the treatment of young adults with first-episode psychosis. It is very helpful to discuss the issue of the illness with the young patient and family, to begin treatment with a lower dose of medication and titrate as needed, and to carefully follow the patient and address any side effects.

The data regarding treatment of first-episode schizophrenia come primarily from trials of second-generation antipsychotic medications. Because the medications had already been approved for adults, the first-episode studies were comparisons either with first-generation medication (haloperidol) or with other second-generation medications. Although the major outcome measure in these studies was effectiveness, rating scales were also included. The trials performed in young adults with early-stage schizophrenia are reviewed in this section, and the key findings are summarized in Table 8–4.

Risperidone

In an effort to determine the efficacy and safety of risperidone in youths with first-episode schizophrenia, Schooler et al. (2005) designed an effectiveness study comparing lower dosages of risperidone (3.3 mg/day) and haloperidol (2.9 mg/day). The main specific aim was measuring effectiveness by recording duration of treatment. Patients treated with risperidone had twice the time to relapse compared with the haloperidol group. Of interest was the similarity of the groups on rating scale measures. Extrapyramidal side effects were more pronounced in the haloperidol group compared with the risperidone group; however, more subjects in the risperidone group had elevated levels of prolactin.

Olanzapine

Olanzapine was the second atypical antipsychotic medication to be tested in first-episode schizophrenia (Lieberman et al. 2003), and like risperidone (Schooler et al. 2005), it was compared with haloperidol. Although olanzapine and haloperidol were associated with comparable symptom reduction during the course of the study, olanzapine 10.2 mg/day was superior to haloperidol 4.82 mg/day in two secondary measures: patients treated with olanzapine were less likely to discontinue treatment, and had increased remission rates, compared with those given haloperidol. Extrapyramidal side effects were less prevalent in patients treated with olanzapine compared with those treated with haloperidol; however, olanzapine carried a higher propensity for weight gain and metabolic side effects (Lieberman et al. 2003).

TABLE 8–4. First-episode schizophrenia antipsychotic trials in young adults

Study	*N*	Age range (mean), years	Format	Drug and dosage, mean and range (mg/day)	Measures	Outcomes	Adverse effects
Schooler et al. 2005	555	16–45 (25.4)	Double-blind, randomized, controlled, flexible-dose trial	RIS 3.3 HAL 2.9	1. Relapse 2. Psychopathology 3. Safety 4. Quality of life 5. Neurocognitive functioning	No significant between-group difference was found in overall discontinuation or in reason for discontinuation. Slightly more than 75% of patients in each group improved clinically. RIS group had significantly fewer relapses than HAL group. Time to relapse was significantly	EPS were more frequent and severe in HAL group. Weight gain was more common in RIS group on treatment initiation. However, at endpoint, weight gain was no longer different between groups.

TABLE 8–4. First-episode schizophrenia antipsychotic trials in young adults *(continued)*

Study	*N*	Age range (mean), years	Format	Drug and dosage, mean and range (mg/day)	Measures	Outcomes	Adverse effects
Lieberman et al. 2003	263	16–40	Randomized, double-blind trial	OLZ 5–20 HAL 2–20	1. Psychopathology 2. Psychosocial measures of social and vocational function and quality of life 3. Neurocognitive function 4. Brain morphology and metabolism	The 12-week acute phase was completed by 68% of OLZ subjects and 54% of HAL subjects.	OLZ-treated patients experienced more weight gain than HAL-treated patients. However, OLZ-treated patients experienced less akathisia and a lower rate of treatment-emergent parkinsonism than HAL-treated patients.

TABLE 8–4. First-episode schizophrenia antipsychotic trials in young adults *(continued)*

Study	*N*	Age range (mean), years	Format	Drug and dosage, mean and range (mg/day)	Measures	Outcomes	Adverse effects
EUFEST (European First Episode Schizophrenia Trial) 2008	498	18–40	Open, randomized, controlled trial	HAL 1–4 AMI 200–800 OLZ 5–20 QUE 200–750 ZIP 40–160	Primary outcome measure: All-cause treatment discontinuation	The number of patients who discontinued treatment for any cause within 12 months was 63 (Kaplan-Meier estimate 72%) for HAL, 32 (40%) for AMI, 30 (33%) for OLZ, 51 (53%) for QUE, and 31 (45%) for ZIP. Atypical agents showed lower risk of any-cause discontinuation rate	Parkinsonian side effects were more frequent with HAL than other atypicals. Weight gain was greatest in OLZ group and least in HAL and ZIP groups. Anticholinergics were most often needed with HAL and AMI. Antidepressants were most frequently needed with OLZ.

TABLE 8–4. First-episode schizophrenia antipsychotic trials in young adults *(continued)*

Study	*N*	Age range (mean), years	Format	Drug and dosage, mean and range (mg/day)	Measures	Outcomes	Adverse effects
McEvoy et al. 2007	400	16–40	Randomized, double-blind, flexible-dose, multicenter study	OLZ 2.5–20 QUE 100–800 RIS 0.5–4	Primary outcome measure: All-cause treatment discontinuation, as reflected by proportion of patients who discontinued from study prior to 52 weeks of treatment	Overall, 70.3% of patients discontinued. QUE was not inferior to OLZ or RIS. The median times to all-cause discontinuation did not differ significantly.	OLZ group showed most frequently drowsiness, weight gain, and insomnia. QUE group showed daytime drowsiness, increased sleep hours, dry mouth, and weight gain. RIS group showed daytime drowsiness, menstrual irregularities, sialorrhea, and weight gain. Percentage of patients with weight gain was greater in [illegible].

Comparison Study of Second-Generation Antipsychotics

In a blinded comparison, McEvoy et al. (2007) reported equal efficacy based on all-cause treatment discontinuation for olanzapine (68%), quetiapine (71%), and risperidone (71%) in young adults early in the course of psychotic illness. Furthermore, reductions in the total PANSS scores were similar for the three medications. Mean modal dosages in the study were quetiapine 506 mg/day, risperidone 2.4 mg/day, and olanzapine 11.7 mg/day. In assessments at 52 weeks into the study, weight gain of ≥7% was seen in 80% of olanzapine patients, 57.6% of risperidone patients, and 50% of quetiapine patients. The sensitivity of young people to second-generation antipsychotic treatment and the need to address weight and metabolic gains were reported. When an initial treatment using the second-generation medications is being considered, symptom reduction was noted to be similar in these patients. It would also be important to test these novel agents in first-episode patients, because the effect may be more robust than in individuals with chronic schizophrenia.

Aripiprazole

To address the effects of aripiprazole in first-episode patients with schizophrenia, a larger aripiprazole versus haloperidol study was analyzed, selecting out patients with early-stage schizophrenia (Girgis et al. 2011). In this evaluation, response rates (50% reduction of PANSS scores) were higher and movement disorder side effects were lower for the early-stage patients taking aripiprazole than for those taking haloperidol.

Clozapine

Studies in the early stages of schizophrenia have examined clozapine as a first-line treatment, but clozapine was not found to provide an advantage (Woerner et al. 2003). However, one study found that of the 20%–25% of first-episode patients who did not respond after two trials with second-generation antipsychotics and then tried clozapine, 75% experienced significant symptom reduction in this early stage of illness (Agid et al. 2007).

In young adults, clozapine is reserved for use only after treatment failure with two other antipsychotic medications (Moore et al. 2007). Notably, in addition to causing weight gain and other side effects that occur with atypical antipsychotics, clozapine carries the risk for agranulocytosis. Complete blood count with differential must be monitored during treatment to prevent neutropenia and subsequent life-threatening infection. Cases of neutropenia are recorded in national registries to prevent a patient with this adverse reaction from being prescribed clozapine at a later date.

Psychosocial and Evidence-Based Therapy Intervention

In addition to specific medication management strategies, a comprehensive psychosocial approach enhances outcome for prodromal, first-episode, and newly diagnosed schizophrenia patients. Most of the psychosocial interventions have been demonstrated to work in adult patients and have been effective in young people with some modifications.

Cognitive-Behavioral Therapy

Even though medications rapidly and effectively reduce symptoms in early stages of schizophrenia, patients often do not return to their premorbid level of functioning. CBT, both in individual and in group

settings, helps patients learn coping mechanisms to mitigate existing symptoms and improve social functioning. Patients have often experienced a decline in social and occupational functioning prior to their first psychotic episodes. They also may not have age-appropriate coping skills and often are socially isolated.

Evidence continues to build for the use of CBT in first-episode psychosis. The majority of psychosocial deterioration that accompanies psychotic disorders occurs during the first few years of illness (Crumlish et al. 2009; Wykes et al. 2011).

Additional evidence supports the use of CBT in the prodromal stage. Three key studies have evaluated the efficacy of CBT in this stage (Fusar-Poli et al. 2012; McGorry et al. 2002b; Morrison et al. 2004). All three found CBT to be an effective intervention to reduce the rate of transition to psychosis. CBT at this stage of illness focuses on development of a shared list of problems and possible solutions. Standard CBT techniques include examination of advantages and disadvantages associated with particular ways of thinking or behaving. Patients consider the evidence for particular beliefs, identify inconsistencies with reality, and generate alternative explanations. Patients then use behavioral experiments to evaluate beliefs.

Family Group

Studies in adults with schizophrenia have shown the advantages of psychoeducation groups in preventing relapse (Hogarty et al. 1986); studies on family therapy for first-episode psychosis show similar results (Fjell et al. 2007). Families are often the primary social network for first-episode psychosis patients. Families also bear the majority of symptom management over time. Psychoeducation for families and caregivers, as well as individual family therapy focused on reduction of emotional intensity in the home, has been shown to reduce both the number and the length of hospitalizations (Lenior et al. 2001). Family intervention reduces morbidity in early-stage psychosis as well as episodes of relapse, or second-episode psychosis.

An important issue in applying multifamily group therapy for parents of first-episode patients with schizophrenia is not only the reduction in relapse for patients but also the beneficial effects it provides the family. The onset of schizophrenia in the family is very stressful and can often lead to parents feeling isolated; therefore, a group with other parents going through a similar challenge is helpful (Schulz et al. 2002). Following the curriculum-based groups addressing information about schizophrenia, lectures on medications, and discussion of therapies, many families become involved in support groups or National Alliance on Mental Health functions.

Cognitive Remediation

Cognitive remediation is an emerging component in comprehensive treatment of first-episode psychosis. *Cognition* broadly refers to ways an individual may process and interact with information. During a psychotic episode, working memory, attention, abstract reasoning, visual processing, and verbal process are affected. Cognitive remediation focuses on improving cognitive skills, without focus on discrete knowledge. Improving cognitive skills allows patients to reach higher levels of social, vocational, and educational achievement. Although medication can be helpful for gross attentional impairment in psychosis, the majority of cognition must be improved with skill training intervention (Medalia et al. 2009).

Cognitive remediation can be provided after acute stabilization. At that time, cognitive deficits have been identified and typically impair functioning. Because of

length of stay and acuity of inpatient admissions, cognitive remediation is best delivered in an outpatient setting.

Cognitive remediation can be offered through a rehabilitation model or day treatment program in groups. Rehabilitation focuses on improving cognitive, emotional, and social variables. Training focuses on skill building by providing tools to enhance a patient's ability to function independently.

A treatment program typically consists of a functioning group of six to eight patients, with rolling admission. Group work enhances both motivation and interpersonal skills. Rolling admission ensures that senior members can orient new trainees. All patients work independently on personal tasks at their own pace. Patients can help one another if needed, but patients primarily function on their own. Patients participate in sessions at least twice a week, for 60–90 minutes per session. The majority of the session involves computer-based skill training, with the remaining time spent discussing how computer-based training has been useful in real life.

In each session, patients use a folder designated to their individual learning course. During each session, patients use their folder to keep track of different computer-based lessons they have completed. Patients are briefly oriented to the computer and software, depending on their level of comfort with the technology. Patients then complete a structured computer-based learning objective focused on memory, attention, processing speed, or problem solving. The group setting addresses social cognition. Group moderators observe, offer encouragement, and intervene only minimally. Computer lessons are quite structured in the beginning, focusing on identified realms of existing cognitive deficit. As patients progress through sessions, tasks become more complex.

A Medical Home for First-Episode Patients

A program coordinator is important to early intervention services for those experiencing their first episode of psychosis. Without coordination of care between multiple facets of intervention, recovery can be difficult. Comprehensive care for a young person experiencing a first episode includes medication management; psychotherapy (individual and/or group); family education and involvement; primary care medical services for comorbidities; and educational, vocational, and occupational services. Early in the disease, families are often in the midst of a highly volatile interpersonal state. During the early disease process, families are in need of a "point person" who is readily available to assist in problem solving and providing counsel.

In the early stages of illness, the young patient may be reluctant to involve the family in his or her care. This reluctance is often due to paranoia involving those with whom the patient is the closest. In an effort to keep the family unit intact, while still engaging the young person in treatment, the psychiatrist can align with the patient, and the care coordinator can continue to educate and support the family. In most cases, as the illness improves, the young person will reestablish the connection with his or her family of origin. Preservation of this relationship is essential for strong treatment engagement.

Recovery After an Initial Schizophrenia Episode Project

The programmatic approach to early-stage or first-episode schizophrenia is now being assessed by the NIMH-sponsored Recovery After an Initial Schizophrenia Episode (RAISE) project, in which

the younger patient is treated with pharmacotherapy, as well as specific psychosocial approaches such as individual resilience, family psychoeducation, and supported employment/education. This important project will add significant information to overall program planning.

Prevention of Adverse Outcomes

In addition to providing patients with the best and most up-to-date resources available, clinicians need to try to prevent adverse outcomes. Suicide, treatment disengagement, and substance abuse are all preventable and detrimental results of treatment failure.

Suicide

Suicide is a tragic outcome of mental illness. Suicide rates worldwide are estimated at one death every 40 seconds and one attempt every 2 seconds (World Health Organization 2007). Among individuals with psychotic illness, the rates of suicide are strikingly high. It is estimated that one-third of all suicides in individuals with mental illness are associated with psychotic disorders (Heilä 1999). According to Heilä et al. (2005), suicides in first-episode psychosis would account for 5% of national yearly suicides (Falcone et al. 2010).

Suicide is most common in the first few years after diagnosis. Two percent of patients commit suicide within 2 years of a first-episode psychosis diagnosis (Krausz and Müller-Thomsen 1993), and 75% of the suicides take place within several months of hospital discharge (Craig et al. 2006).

Any patient who develops severe hopelessness, depression, or preoccupation with suicidal ideation needs to be monitored very closely. Early intervention can reduce suicides in first-episode patients. Special attention to patients should be given during transition from prodrome to psychosis, during early recovery, and at relapse.

Medication Nonadherence

Medication nonadherence is a common issue in general medicine as well as psychiatry. Adherence seems to be particularly difficult when medications aim to prevent relapse (Blackwell 1972). It is helpful to discuss problems and side effects of medication. It is also helpful to engage family members and to obtain collateral information regarding adherence (Velligan et al. 2009). Adherence is essential in psychosis. In one study, poor adherence resulted in 69% relapse rates, whereas good adherence produced only 18% relapse rates (Morken et al. 2008). Additionally, if patients are not honest about their daily medication compliance, doses of neuroleptics may be inappropriately increased because response is poor (Velligan et al. 2009).

Use of long-acting injectable risperidone may improve patient adherence. Weiden et al. (2012) reported that first-episode patients agreed to this form of medication at a high rate (78%) and that the treatment was useful.

Substance Use Disorders

Substance use disorders are a serious risk factor for patients with schizophrenia; 37%–70% of first-episode patients are misusing a substance. Stimulants such as amphetamines are frequently misused by adolescents and young adults. This misuse can lead to a substance-induced psychosis or precipitate early-stage schizophrenia. Recent research has demonstrated an increased risk of developing schizophrenia with substance use disorders. Cannabis misuse also exacerbates ongoing psy-

chotic symptoms and produces a monumental barrier to successful symptom remission (Grech et al. 2005).

New research has pointed to temporary breakdown of cognition in cannabis users without psychosis. This cognitive breakdown can lead to long-term psychosis (Harding et al. 2012). It was also found that patients with schizophrenia and cannabis abuse had altered functional neuroimaging findings compared with schizophrenia patients without cannabis use.

Conclusion

First-episode psychosis is an evolving field of study that has helped in reducing the duration of untreated psychosis. Substantial research efforts have led to significant hope in changing the outlook of a once-devastating diagnosis. The majority of patients with first-episode psychosis will reach clinical remission (Alvarez-Jiménez et al. 2011); however, relapse rates remain as high as 80% within 5 years. Each relapse increases the risk of developing persistent psychotic symptomatology (Stephenson 2000).

Comprehensive first-episode programs have been shown not only to improve time to remission but also to prevent future relapse. Comprehensive treatment includes rapid detection and early initiation of antipsychotic medication management as well as psychosocial intervention. Patients treated in comprehensive programs, with specialist care, had lower relapse rates than treatment as usual in nonspecialist centers. Specialty first-episode programs that included individual and family-based cognitive therapies, which focused on relapse prevention, were also more efficacious at maintaining symptom remission.

Ultimately, a combination of early engagement, short duration of untreated psychosis, strong therapeutic bond with the treatment team, frequent follow-up, provision of cognitive-based therapies for family and individuals, and strong case management results in the best treatment outcome for first-episode patients.

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CHAPTER 9

Toward a Dimensional Understanding of Psychosis and Its Treatment

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Psychosis is a mental state characterized by a set of perceptual, thought disorder, and cognitive symptoms and constructs that manifest themselves in several psychiatric diseases, such as schizophrenia and mood disorders, but also in some neurological disorders, such as epilepsy, Huntington's disease, and Alzheimer's disease, and in some medical diseases, especially endocrinological and metabolic conditions.

Psychotic symptoms are characterized by a combination of hallucinatory experiences, delusional interpretations of reality, and frank thought disorder, often accompanied by thought and behavior disorganization. Psychotic symptoms are experienced by individuals as real cognitive and sensory occurrences and involve all sensory modalities (auditory, visual, olfactory, gustatory, and tactile). The most characteristic experience of psychosis is "loss of reality," which represents the psychotic individual's unquestioned perception that his or her symptoms are real occurrences and not pathological mental constructs; this experience occurs particularly in psychiatric psychotic syndromes.

The World Health Organization's International Psychosis Study (Carpenter et al. 1973) investigated whether psychotic symptoms vary around the world in different cultures and regions by examining psychosis in individuals across seven countries; the conclusion was that psychotic symptomatology spans continents, languages, and cultures with great

similarity, albeit with great interindividual variability.

Several first-person accounts written by brilliant and self-perceptive individuals with psychosis record the nature of psychosis and illustrate the profound loss of reality testing around psychotic experiences. John Nash described the nature of his delusion:

> These ideas just keep coming into my head. I can't prevent it. [I] believe that there is a conspiracy among military leaders to take over the world, and that [I] am in charge of the takeover. [I] secretly feel that I am the left foot of God. And that God is walking on the earth. (qtd. in Nasar 1998, p. 234)

Elyn Saks (2007) detailed her experience of psychotic "disorientation" as follows:

> Consciousness gradually loses its coherence. The "me" becomes a haze.. reality breaks up like a bad radio signal. There is no longer a sturdy vantage point from which to look out, take things in, assess what's happening. No core lens through which to see the world, to make judgments and comprehend risk. Random moments of time follow one another. Sights, sounds, thoughts, and feelings don't go together. No organizing principle takes successive moments in time and puts them together in a coherent way from which sense can be made. And it's all taking place in slow motion. (p. 89)

The clinical manifestations of psychosis are illustrated in these two examples, with evidence of hallucinations, delusions, thought disorder, and disorganization. Psychosis is a *disturbance* of cognition, not a *global loss* of cognitive capacity as seen within dementing illnesses. Indeed, psychosis is a "gain-of-function" symptom, with increased associational productions, bizarre perceptual experiences, thoughts, and established memories with psychotic content. This is in contrast to the dementias, which are "loss-of-function" cognitive disorders, in which memory is reduced and thought processes are altered and frequently diminished. Because psychotic experiences appear entirely real to the person suffering them, it is easy for the individual to act on the psychotic perceptions (i.e., command hallucinations) or the delusional thinking, which can result in bizarre, illogical, or even dangerous behavior.

Psychosis is a broadly expressed symptom set across many diagnoses and can be called an intermediate phenotype or a symptom complex that may have a unique and independent brain network and biology and its own genetic associations. One could argue that the intermediate phenotype of psychosis is a symptom dimension representing a final common pathway of cerebral dysfunction (we would argue that psychosis is secondary to a disorder of learning and memory mechanisms) even though it is generated by diverse etiologies. It is possible to conceive that this symptom set has its own unique and distinctive anatomy, pathophysiology, and molecular targets, as well as treatments, although this has yet to be demonstrated. The Research Domain Criteria (RDoC) system from the National Institute of Mental Health is a leading example of this reorientation. In the RDoC framework, dimensions of normal cognition and affect are the unifying, homogenous units that decompose to generate psychopathology.

Differential Diagnosis and Characteristics of Psychosis

The differential diagnosis of psychosis is carried out by clinicians every day. Often,

psychotic symptoms per se are the same across the categorical diagnoses that are used, but the accompanying mood and cognition symptoms generate the distinctiveness across these diagnoses. *Schizophrenia* is one of the more severe psychotic disorders, with this symptom set expressed pervasively (even though often controlled by antipsychotic medication). In addition to the psychosis, the cognitive dysfunctions are circumscribed in schizophrenia (Hill et al. 2008), with attention, working and declarative memory, and executive functions being most impaired (Stefanopoulou et al. 2009). Also, a negative symptom complex can be present and is characterized by reduced affect expression and awareness, reduced social interactions, and thought and speech paucity; this is not a disturbed mood state, as seen in depression, but rather a blunted or reduced mood experience. Schizophrenia is always described as the psychotic illness with the worst psychosocial outcome (Harvey et al. 2012).

About 50%–60% of people with bipolar I disorder have bipolar disorder with psychosis; these individuals usually express psychotic symptoms only during acute mood episodes, but some of these individuals have extended psychotic manifestations. Contrasted with patients with schizophrenia, however, individuals with bipolar disorder with psychosis are said to have fluctuating mood states with affect dysregulation, better psychosocial function, and reduced deterioration with aging. Major depressive disorder (MDD) with psychosis includes mood-congruent psychotic symptoms that manifest exclusively during severe mood episodes. The psychotic diagnoses within neurological conditions show rather typical psychotic symptoms but with the accompanying stigmata and biomarkers of the disease itself, such as the family history in Huntington's disease, a history of deteriorating memory in Alzheimer's disease, or the seizure disorder that accompanies epilepsy psychosis. Clinical lore suggests that the actual psychotic manifestations differ across psychotic diagnoses. Verification of this claim is not available in a rigorous format; however, there are certainly many examples of mistaken diagnoses across these psychotic presentations, and caution ought to prevail around taking only the psychotic symptomatology into account in generating a diagnosis without looking at the psychosis within the context of more characteristic mood and cognition disease symptomatology.

Genetic Characteristics of Psychosis

Modern genetic studies have identified schizophrenia and psychosis as complex genetic illnesses. Despite early evidence for specific risk genes by diagnosis, the expectation soon dissipated with the realization that, with replication and sufficient power, many genes generate risk for psychosis. Genome-wide association studies indicate that there may be more than 1,000 risk genes for schizophrenia and other kinds of psychosis, each of small effect, suggesting that these disorders are all complex genetic illnesses (Wellcome Trust Case Control Consortium 2007). Moreover, these reports show an overlap in genetic susceptibility across the traditional diagnostic categories, including association findings at the following: neuregulin 1 (*NRG1*), disrupted in schizophrenia 1 (*DISC1*), catechol O-methyltransferase (*COMT*), distroverin-binding protein (dysbindin), D-amino acid oxidase activator (*DAOA G72/G30*), and brain-derived neurotrophic factor (*BDNF*). For example, *NRG1* has been im-

plicated in schizophrenia (Tosato et al. 2005), associated with bipolar disorder (Goes et al. 2009), and linked to clinical phenotypes of bipolar disorder with mood-incongruent psychotic symptoms, as well as with schizophrenia with lifetime manic episodes (Green et al. 2005). This suggests that *NRG1* may confer susceptibility to a specific clinical phenotype with combined features of psychosis and mania. A number of linkage and association studies suggest that *DISC1* may mediate susceptibility to disorders of psychosis spectrum including schizophrenia, schizoaffective disorder, bipolar disorder, and psychotic MDD (Owen et al. 2007). Although this gene has been named "disrupted in schizophrenia," the pedigree in which the *DISC1* translocation was originally observed included cases of both schizophrenia and mood disorders. Recently several independent groups reported associations of *DISC1* with schizoaffective and bipolar disorders, suggesting that *DISC1* may influence susceptibility to psychosis-mood phenotype that cuts across the traditional diagnostic categories (Ekelund et al. 2004; Millar et al. 2000). Dysbindin (dystrobrevin binding protein gene *DTNBP1*) has been extensively studied in schizophrenia (Funke et al. 2004; Numakawa et al. 2004; Schwab et al. 2003), and reports have suggested an association between this gene and a clinical subtype of bipolar disorder with recurrent psychotic symptoms (Raybould et al. 2005). Overall, these findings support *NRG1, DISC1,* and *DTNBP1* as candidate genes contributing to susceptibility to psychosis or a mixed phenotype with features of both psychosis and mood symptoms rather than to DSM-IV schizophrenia (American Psychiatric Association 1994), even though these loci were originally proposed as schizophrenia risk genes. In contrast, *BDNF* and *DAOA G72/G30* appear to be more strongly associated with mood symptoms domain across the traditional DSM-IV diagnoses (Williams et al. 2006).

In addition to the studies of individual candidate genes, linkage studies have identified several chromosomal regions showing associations with both schizophrenia and affective psychosis. These include 1q32, 10p11–15, 13q32, 18p11.2, and 22q11–13 (Badner and Gershon 2002; Bramon and Sham 2001), as well as suggestive linkages to 5q33, 6q21, 8p24, 15q26, 17p12, 18q21, and 20q13 (Park et al. 2004). A recent genome-wide linkage scan in schizoaffective disorder using British and Irish pedigrees with at least one member diagnosed with DSM-IV schizoaffective disorder confirmed the existence of loci that influence susceptibility across the functional psychosis spectrum (Hamshere et al. 2005). This study demonstrated significant linkage at chromosome 1q42 and suggestive linkages at 22q11 and 19p13. The evidence for these linkages was equally contributed by schizophrenia pedigrees (where schizophrenia was predominant among relatives in addition to schizoaffective disorder) and bipolar disorder pedigrees (with higher proportion of affective psychosis). Notably, two candidate genes, *DISC1* and *COMT*, that have been implicated in schizophrenia and, more recently, in bipolar disorder map to 1q42 and 22q11, respectively.

Family studies have provided strong evidence for heritability and familial aggregation of schizophrenia and other psychotic disorders. The lifetime risk for developing schizophrenia increases approximately 8- to 12-fold in first-degree relatives of probands with schizophrenia. First-degree relatives of individuals with bipolar I disorder have elevated rates of bipolar I disorder (4%–24%), bi-

polar II disorder (1%–5%), and MDD (4%–24%). Although it was originally thought that schizophrenia and affective psychoses are inevitably segregated, more recent reports challenge this. Family studies show that schizophrenia and affective psychoses occur together in the same families, suggesting shared familial risk. For example, a large epidemiological study, using a genetically homogeneous population in northeastern Finland (Arajärvi et al. 2006), reported that 16% of siblings of probands with schizophrenia received a diagnosis of psychotic disorder, including schizophrenia (0.5%), schizoaffective disorder (3.3%), bipolar I disorder (1.1%), MDD with psychotic features (2.2%), alcohol-induced (2.2%) and other substance-induced (1.1%) psychoses, delusional disorder (1.6%), and psychotic disorder not otherwise specified (4.4%). Over half (54%) of the siblings in this study had a lifetime diagnosis of any mental disorder, with MDD (15.3%) and anxiety disorders (12%) leading among nonpsychotic illnesses. Other reports have also confirmed that the increased risk for psychotic illness in relatives of persons with schizophrenia does not appear to be confined to schizophrenia alone (Henn et al. 1995; Ivleva et al. 2012a). Also, bipolar illness has been associated with increased risk of schizophrenia in relatives. A large report from mixed schizophrenia/bipolar disorders pedigrees showed that relatives of women with early-onset bipolar disorder had the highest morbidity risks for both bipolar illness and schizophrenia (Vallès et al. 2000). The presence of more than one patient with bipolar disorder in a family increased the risk for schizophrenia nearly fourfold. Schizoaffective disorder occurs at similarly increased rates both in families of probands with schizophrenia and in families of probands with bipolar disorder. In contrast, both schizophrenia and bipolar disorder have been shown to occur at increased rates in relatives of probands with schizoaffective disorder (Maier et al. 1992).

Studies show that the concordance rate for schizophrenia is higher in monozygotic twins (47%–56%) than in dizygotic twins (12%–16%), supporting the heritable nature of psychosis (Gottesman and Shields 1966). It has been observed that the more severe the schizophrenia, the more likely it is for the twins to be concordant for the disorder. Some studies have reported concordance rates for monozygotic twins of over 80% in cases of severe schizophrenia with typical "core" symptoms (Gottesman and Shields 1966). These observations may suggest that the schizophrenia diagnosis includes clinically and etiologically heterogeneous subgroups with various genetic backgrounds. Furthermore, twin studies suggest that the schizophrenia diagnosis in one twin increases risk for both schizophrenia and affective disorders in the co-twin (Cardno et al. 2002; Farmer et al. 1987). A clear overlap in genetic risks for schizophrenia, schizoaffective, and manic phenotypes was reported in a sample of 77 monozygotic and 89 same-sex dizygotic twin pairs, ascertained from the Maudsley Twin Register in London (Cardno et al. 2002). In this study, if one member of a monozygotic twin pair had schizophrenia, there was about an 8% chance of schizoaffective disorder diagnosis in the co-twin and an 8% risk of mania. Furthermore, the maximum monozygotic/dizygotic concordance ratio was produced by a combination of schizophrenia, psychotic affective disorder, schizotypal personality disorder, and atypical psychosis, suggesting that these psychosis spectrum disorders share a genetic background.

Psychosis as a Pathological Deterioration of Learning Memory

We include here an illustration of a mechanistic model of psychosis, albeit speculative, that is aimed at affording a basis for rational treatment development, once it has been modified and verified experimentally. The RDoC-like foundational strategy for this approach is to identify the normal cognition system(s) in the brain whose pathology could generate psychosis (Ivleva et al. 2012b), which would serve as the basis for targeting a rational treatment for the psychosis syndrome. Given the characteristics of psychotic thought, the brain regions implicated in psychotic manifestations, and the response characteristics of the symptoms, we have postulated a connection between abnormal learning and memory as mediated in hippocampus within medial temporal cortex and psychotic symptoms. We review the evidence here.

Traditional neuropsychological studies have documented "global" deficits in declarative memory in individuals with schizophrenia (Ranganath et al. 2008). Declarative memory can be parsed into several distinct memory steps, which include functions like encoding, retrieval, and long-term storage, as well as associative binding within and across memory episodes, memory consolidation, and subsequent generalization to new episodes (Heckers et al. 1998; Preston et al. 2005). Some, but not all, of these processes are altered in schizophrenia. Deficits in the relational component of declarative memory, *relational memory* (RM), are primarily affected; RM is the function by which inferential strategies are used to make new associations across memory episodes for the purpose of flexibly applying information from past experience to novel environments (Ivleva et al. 2012b; Shohamy et al. 2010; Ziethamova and Preston 2010). Notably, it is these RM alterations that can be seen in schizophrenia at the same time as intact associative learning and memory retention (Ongür et al. 2006; Shohamy et al. 2010). Fortunately, functional magnetic resonance imaging (fMRI) studies in healthy individuals have mapped a network of brain regions that subserve RM; these include many regions, especially the hippocampus and prefrontal cortex, that are already implicated in schizophrenia itself (Giovanello et al. 2004; Kirwan and Stark 2004; Ranganath et al. 2008; Staresina and Davachi 2009; Zeithamova and Preston 2010). Therefore, RM may itself be a "biomarker" for the clinical phenotype of psychosis.

An interesting question is how we can understand the alterations in RM in schizophrenia. The hippocampus is known to be associated with RM formation, based originally on assessment of the patient H.M.; RM is altered in schizophrenic psychosis, showing structural, functional, and molecular pathology, all of which suggest a contribution of hippocampal pathology to schizophrenia (Figure 9–1). Specifically, psychosis is associated with increases in basal hippocampal activity (as measured by regional cerebral perfusion) and reduced neural activation during RM processing (Tamminga et al. 2010). Each of the hippocampal subfields (dentate gyrus [DG], cornu amonius 3 [CA3], cornu amonius 1 [CA1], and subiculum) has unique and complementary functions in memory formation and are connected, in part, by a unidirectional pathway that mediates normal and relational memory. At the start of this trisynaptic pathway, the DG functions to distinguish between new and already established memories through a process of

pattern separation. The next subfield, CA3, is known to carry out *pattern completion* function, where associations are made to existing memories from incomplete stimuli (Abraham and Bear 1996; Kremin and Hasselmo 2007; Pelkey and McBain 2008). Human in vivo imaging changes, as well as postmortem molecular signals, suggest that the process of pattern separation is reduced in schizophrenia, encouraging the identification of familiar stimuli as novel, while pattern completion is enhanced, leading to pathologically increased associations and the creation of false, illogical memories, resulting in psychotic thoughts and memories. It is plausible (and the hypothetical basis of our studies) that these hippocampal alterations underlie both RM deficits in schizophrenia and the psychotic manifestations.

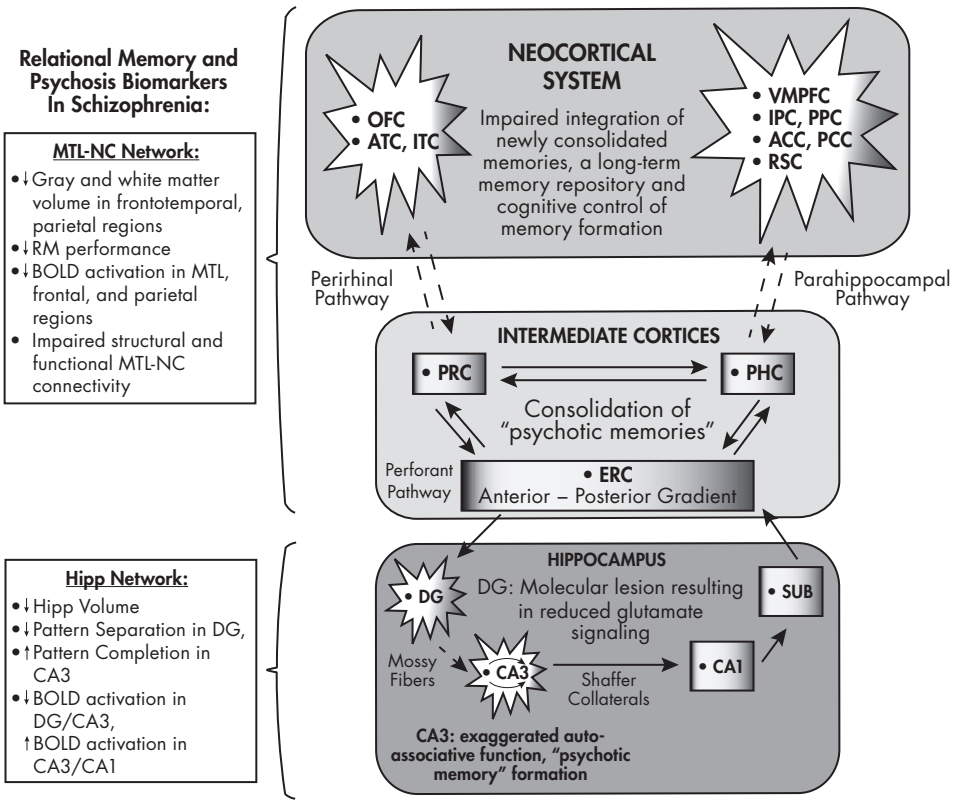

FIGURE 9–1. A relational memory and psychosis model of schizophrenia involving hippocampal-neocortical network.

Note. ACC = anterior cingulate cortex; ATC = anterior temporal cortex; BOLD = blood oxygen level dependent; CA1 = cornu amonius 1; CA3 = cornu amonius 3; DG = dentate gyrus; ERC = entorrhinal cortex; Hipp = hippocampal; IPC = inferior parietal cortex; ITC = inferior temporal cortex; MTL = medial temporal lobe; NC = neocortical; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; PHC = parahippocampal cortex; PPC = posterior parietal cortex; PRC = perirhinal cortex; RM = relational memory; RSC = retrosplenial cortex; SUB = subiculum; VMPFC = ventromedial prefrontal cortex.

Within this framework, it is conceivable that psychosis is dependent on a pathological increase in the level of neuronal function in CA3, which exceeds the associational capacity of this subfield and results in mistaken and false associations,

some with psychotic content, which then get consolidated into memory, albeit with psychotic content. These psychotic memories utilize normal declarative memory pathways, including hippocampal and neocortical regions, even though the memories have psychotic content. The hippocampus forms a broad network of connections with brain associational cortices and is organized into a complex hierarchical system (Small et al. 2011). This network is thought to be a basis for many cognitive processes, including long-term memory formation (Squire and Zola 1996). The hippocampus and its immediate neighbors uniquely contribute to memory formation by creating conjunctive representations, binding multiple elements into a unitary memory representation, as well as memory consolidation, whereas the neocortex provides a long-term memory repository and cognitive control of memory formation (O'Reilly and Rudy 2001; Ranganath et al. 2008). Building on several recent theoretical models (Squire and Zola 1996; Tamminga et al. 2010), we hypothesize that in schizophrenia, impaired memory representations are generated within the hippocampal subfields, based on failed glutamate signaling and decreased pattern separation function in DG, and increased auto-associative memory function in CA3 (see Figure 9–1).

Treatments for Psychosis Based on Hypotheses of Hippocampal Pathology

It is no secret that identifying molecular targets for novel treatment development that are firmly associated with a psychiatric diagnosis, especially psychosis, has met with great difficulty in psychiatry. No truly novel approaches to treat psychosis have been developed for over half a century. Novel treatment development has stalled for lack of indicated directions. Although pharmaceutical companies are very good at developing probes for a specific target, the development of the neural targets for manifestations like psychosis is left to the field of psychiatry and its related neuroscience allies. The difficulty in developing mechanistic models for psychiatric diseases may derive, in part, from using incorrect disease constructs—namely, categorical diagnoses defining syndromes—that do not describe biologically homogeneous groups. Recently, clinical scientists have begun to examine alterations in *dimensions* of cognition or affect for clues to neural mechanisms of broad and common psychopathology, rather than diagnoses of neuropsychiatric diseases. We hypothesize that within the large diagnostic categories that we currently use are pooled several, if not many, homogeneous disease–like groups that have common mechanisms and that can be the target of both shared and distinct optimal treatment approaches.

The current pharmacological treatments for schizophrenia are detailed in Chapter 11, "Pharmacological Treatment of Psychosis," and the use of cognitive remediation for schizophrenia is detailed in Chapter 10, "Psychosocial Treatments for Chronic Psychosis," based on the current disease formulations. Antipsychotic drugs are effective for psychosis independent of formal diagnoses, suggesting that both psychosis and the effects of these drugs are directed at targets downstream from selective disease pathophysiology.

The reason for seeking and verifying new disease formulations is to uncover novel treatments. If we are able to use this learning and memory model for psychosis and to verify the psychosis mechanism we have proposed, or something like it, it

would allow us to both use the mechanism to identify new treatments and use related biomarkers to verify the effects of novel treatment approaches. Hippocampal perfusion might be the single most striking and novel biomarker for marking psychosis; it would be a marker analogous to elevated blood sugar for diabetes. We presume, although we do not have data to verify this, that correcting this particular underlying individual biomarker of the psychosis will also improve clinical symptoms in an individual with psychosis. The biomarker would be designed to generate disease-modifying agents and to define a treatment endpoint (i.e., individual antipsychotic action) as well. If this dimensional approach is correct, then we will have to change our conceptualization (although not our practice) of drug treatments for schizophrenia by using these treatments dimensionally and not diagnostically. Because the target (hippocampal hyperperfusion, in this case) is concrete and can be re-created in animals, it would provide animal targets for drug development. Considerable work still has to be done to verify this biomarker, and it is premature to consider it as such. Nonetheless, within this model, treatment approaches for psychosis should seek to reduce neuronal activity in hippocampus as it is indicated by cerebral perfusion. We should be able to document high hippocampal perfusion during florid psychosis and its reduction with antipsychotic drug. A focused study of the mechanisms for increased perfusion in psychosis will offer specific molecular targets for psychosis itself.

In summary, in this chapter we have suggested one kind of scenario for future drug development for psychosis. That scenario is based on a mechanistic understanding of how psychosis occurs. We suggest that alterations in hippocampal learning and memory mechanisms could generate psychosis and that treatment for psychosis control might optimally be directed toward reducing activity in the hippocampus itself. It is a focus on building biomarkers for brain diseases that will drive this kind of a rational process for treatment development in the future.

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CHAPTER 10

Psychosocial Treatments for Chronic Psychosis

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Although antipsychotic medications are the mainstay of care for chronic psychotic disorders such as schizophrenia, pharmacotherapy alone produces only limited improvement in negative symptoms, cognitive function, social functioning, and quality of life. Many patients continue to suffer from persistent positive symptoms and relapses even when they adhere to prescribed medications. Increasingly, community-based care is replacing hospital-based care and shifting the responsibility of managing illness-related burden to the patients and their family members. This chapter highlights the need for multimodal care, including psychosocial therapies as adjuncts to antipsychotic medications to help alleviate symptoms; to improve adherence, social functioning, and quality of life; and to prevent relapse. In this chapter, we review evidence that has accumulated on the efficacy of the main modalities of psychosocial treatment, such as cognitive-behavioral treatment, social skills training, cognitive remediation, and psychoeducational coping-oriented interventions, and also comment on other promising approaches.

Historical Overview

Psychotherapeutic treatments in schizophrenia have evolved over the past century in tandem with the conceptual models prevalent at the time (Figure 10–1 and Table 10–1). Before the early twentieth century, few psychosocial interventions were in place other than custodial care. The so-called first-generation approaches that appeared were those that were either unrelated or only indirectly related to the core disturbances in schizophrenia or its pathophysiology. Psychoanalytic models of the origins of psychosis in the first half of the twentieth century led to psychodynamic approaches to treatment. Interpersonal and family theories of psychosis in the 1960s and 1970s led to major role therapy and family psychoeducation. With increasing knowledge about

the nature of cognitive and social cognition deficits, as well as affective dysregulation, in schizophrenia in the 1980s and 1990s, disorder-relevant, second-generation psychotherapies were developed that more directly targeted the core aspects of disease manifestations and pathophysiology; these included social skills training, cognitive-behavioral therapy, personal therapy, and cognitive remediation (Hogarty 2002). Although some of these interventions have an evidence base in the literature (Table 10–2), others, such as metacognitive therapies, have yet to be systematically investigated but are promising.

The first generation of psychosocial treatments for schizophrenia were largely atheoretical, were nonspecific to disorder and phase, and focused primarily on the pressing need of supporting the large influx of patients leaving the state hospitals in the community. As chlorpromazine, major role therapy, assertive community treatment, family psychoeducation, and other first-generation interventions helped to facilitate discharge readiness and increase community tenure, psychosocial interventionists turned their attention to maximizing patient functioning, adjustment, and quality of life in the community, which became the focus of second-generation psychotherapies for schizophrenia.

Nature of Schizophrenia: Considerations for Psychotherapy

Understanding the nature of schizophrenia is critical for placing psychotherapeutic treatments in the appropriate perspective (Tandon et al. 2010). The construct of schizophrenia has evolved over the past century since Emil Kraepelin's original demarcation of this illness from manic-depressive insanity; the "core" disturbance in this illness was one of chronicity and functional decline, features that led to its originally being named *dementia praecox*. Eugen Bleuler emphasized the disturbances in associations, characterized by "splitting" of mental functions, and Kurt Schneider considered disturbances in ego boundaries leading to characteristic ("first-rank") symptoms of delusions and thinking disturbances as being central to the illness. In the 1950s and 1960s, psychoanalytic conceptualizations of disease causation were dominant, leading this illness to be viewed as comprising psychobiological "reactions" to the manifold interpersonal and familial stresses of the individual's life. DSM-III (American Psychiatric Association 1980) combined several of these features and developed operational criteria that vastly improved reliability of diagnosis. Over the past two decades it has become increasingly clear that cognitive deficits and distortions are central to schizophrenia and that these impairments strongly predict functional disability. The disease is thought to be multifactorially caused, with several risk genes interacting with psychosocial and biological stresses. As discussed in the following subsections, four key aspects of the nature of the illness are of importance in considering psychotherapeutic treatments.

Course of Schizophrenia Evolves in Stages

The course of schizophrenia is characterized by a sequence of phases. The *premor-*

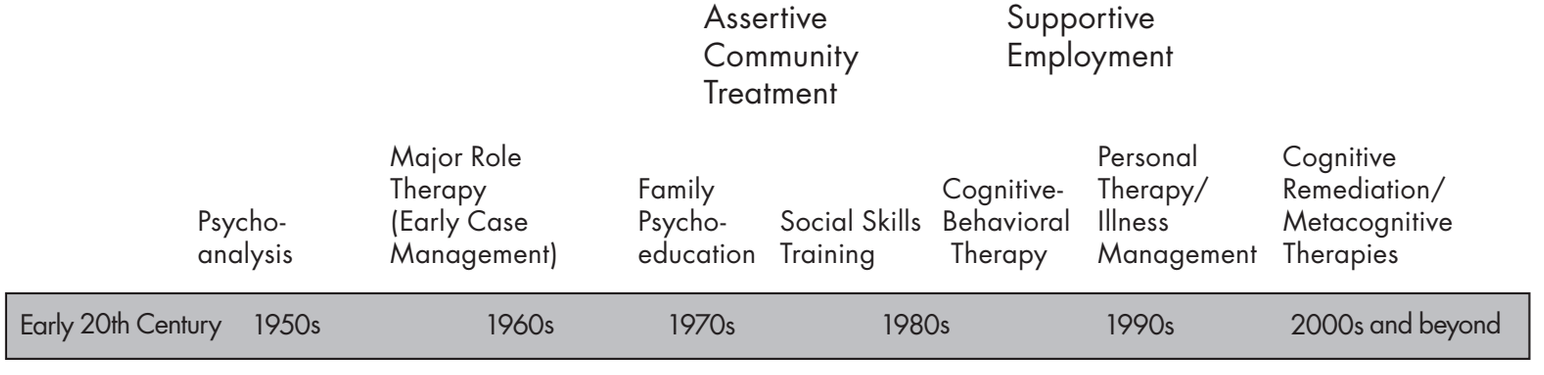

TABLE 10–1. Psychotherapeutic approaches in schizophrenia

Approach	Primary goal
Psychoanalytic therapy	Correcting faulty defenses, regression to earlier developmental stages
Supportive therapy	Addressing impact of illness on life issues
Reality adaptive therapy, major role therapy	Providing early case management and support
Psychoeducation and coping-oriented interventions	Increasing illness awareness
Family psychoeducation	Modifying primary environmental stress
Social skills training	Correcting maladaptive behavioral excesses or deficits
Cognitive-behavioral therapy	Correcting faulty cognitive schemata (i.e., targeting "what" a person thinks)
Personal therapy and illness management	Promoting self-monitoring and adaptive control of early symptoms
Cognitive remediation	Restoring cognitive and social cognitive abilities
Metacognitive and mindfulness-based therapies	Correcting metacognitive biases (i.e., targeting "how" a person thinks)

TABLE 10–2. Meta-analyses of psychotherapeutic interventions in schizophrenia with available effect sizes

Treatment modality	Outcome measure	Effect size (Hedges *g*)	References
Cognitive-behavioral therapy	Positive symptoms	0.35–0.65	Zimmerman et al. 2005; Pfammater et al. 2006; Wykes et al. 2008
Cognitive remediation	Cognitive functioning Social functioning	0.11–0.98 0.36–0.51	Pilling et al. 2002b; Wykes et al. 2011
Psychoeducation	Relapse (2 years)	0.17–0.56	Pitschel-Walz et al. 2001; Pilling et al. 2002a; Lincoln et al. 2007
Social skills training	Skill acquisition Community functioning	0.76–1.43 0.51	Benton and Schroeder 1990; Pilling et al. 2002b; Kurtz and Mueser 2008

Source. Adapted from Tandon et al. 2010.

bid phase is associated with cognitive and social difficulties dating back to early childhood in many cases. The *prodromal phase* is characterized by cognitive and social declines and mood, thought, and personality changes, as well as subthreshold psychotic-like symptoms beginning insidiously over time. The *psychotic phase* is heralded by florid positive symptoms such as hallucinations and delusions, and poor insight. That phase is followed by a *transitional (or recovery) phase,* lasting months to years, which is characterized by ambivalence about treatment, comorbid depression and anxiety, and a tendency to frequent stress-induced relapse before stabilization. The *stable, chronic (or residual) phase* is characterized by persistent negative symptoms, cognitive deficits, and remissions and exacerbations in psychotic symptoms. The primary goals of psychotherapy vary across the phases, as described in Table 10–3: reduction of prodromal symptoms and prevention of psychosis are the key goals in the prodrome; reduction of psychosis severity and duration and prevention of relapse are central to the psychotic phase; prevention of relapse and treatment of comorbid symptoms are critical to the transitional phase; and rehabilitation and community reintegration are the core goals of the chronic phase. Psychotherapeutic treatments are phase specific and therefore need to be tailored to the patient's current main problems (Figure 10–2).

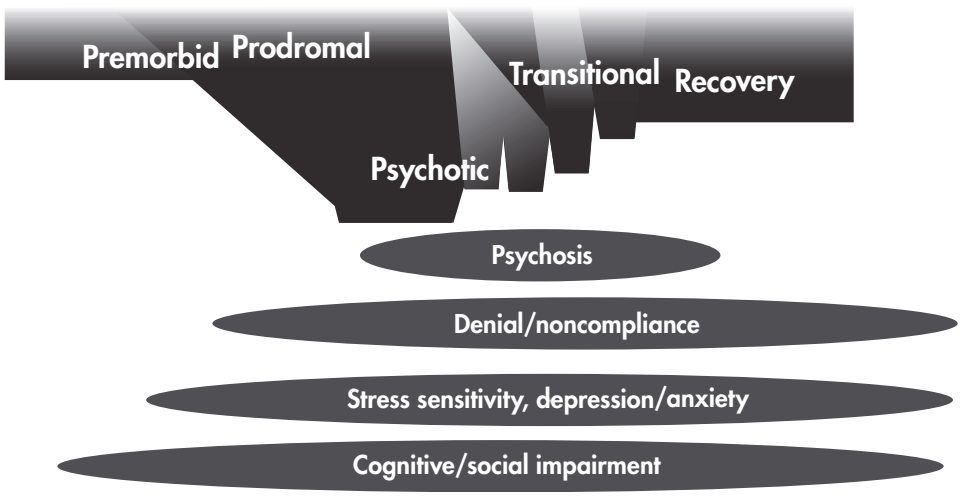

FIGURE 10–2. Phases of schizophrenia and the evolving goals of psychotherapeutic treatment.

Cognitive as Well as Affective Impairments Are Core Aspects of Psychopathology

The clinical manifestations of schizophrenia are manifold, with several key symptom domains. *Cognitive deficits* in schizophrenia are highly prevalent, are pervasive across a wide range of domains (including working memory, executive functions, verbal memory, and social cognition), robustly distinguish patients with schizophrenia from healthy comparison subjects (with an effect size of

TABLE 10–3. Tailoring psychotherapeutic interventions to the phase of schizophrenia

Phase	Prodromal	Psychotic	Transitional (recovery)	Chronic (residual)
Main treatment goal	Reduce prodrome symptoms and duration; prevent psychosis	Reduce psychosis symptoms and duration; prevent relapse	Prevent relapse; treat comorbid symptoms; begin reintegration to community	Reintegrate to community and rehabilitate
Supportive therapy	X	X	X	X
Individual/family psychoeducation	X	X	X	X
Cognitive-behavioral therapy	X	X	X	X
Illness management (personal therapy)		X	X	X
Motivational interviewing (compliance therapy)		X		
Cognitive remediation			X	X
Social skills training			X	X
Supportive employme				X

about 1), and strongly predict functional outcome (Green 1996). Cognitive deficits in schizophrenia are also persistent, being present in the premorbid as well as prodromal, early, and chronic phases of the illness. Impairments in social cognition, such as theory-of-mind deficits, are particularly potent predictors of outcome (Penn et al. 2008).

Disturbances in affect are also a core feature of schizophrenia. Depressive and anxious moods, as well as blunted affect, are highly prevalent throughout the course of the illness. Neuroimaging studies suggest abnormalities in structural and functional integrity of the amygdala, a key component of the emotional circuits. Response of the amygdala to emotional stimuli, as compared with neutral stimuli, is attenuated in schizophrenia; abnormal reactivity of the amygdala along with prefrontal impairment may result in impaired emotion recognition and expression (or flattening of affect). By contrast, hyperactive dopamine systems in the context of a failure of prefrontal regulation may cause increased autonomic arousal and aberrant emotional salience to nonthreatening stimuli, which are characteristic of psychosis (Aleman and Kahn 2005); this situation leads to the emotional "paradox" in schizophrenia, wherein decreased emotional expressivity is coupled with hyperarousal especially in paranoid patients. Recognition of this aspect of affect disturbance and its relation to symptoms and impairments in schizophrenia is critical for appropriately tailoring psychotherapeutic approaches.

Pathogenesis Involves Developmental Derailments

Schizophrenia typically begins in adolescence, but many individuals have premorbid alterations dating back to early childhood, suggesting that this illness may have its origins in altered brain development. Early brain adversity and "late" brain developmental processes may interact with adverse hormonal, biochemical, and psychosocial demands of adolescence and early adulthood, predisposing to the illness. The adolescent onset of schizophrenia may be related to a "plasticity switch," perhaps due to excessive loss of synapses, which may result in inefficiency of brain function. This diminished plasticity may in turn underlie social and nonsocial cognitive deficits, leading to preadolescent processing styles that fail to meet the adaptive and "gistful" abstraction requirements of adult cognition (Keshavan and Hogarty 1999). Psychotherapeutic interventions such as cognitive remediation approaches need to target these altered developmental processes.

Risk and Diathesis Are Key to Causation

Although the etiology of schizophrenia remains unknown, an important early conceptualization of schizophrenia is that the disease reflects an interaction between a premorbid vulnerability and the individual's response to stress. The stress-induced affective and psychomotor hyperarousal in the vulnerable individual might underlie the cognitive disruptions that serve as precursors to or early symptoms of psychosis. Episodes of the illness occur when the person's vulnerability exceeds a threshold that can homeostatically cope with the stress; when the episode ends, the person returns to the state of premorbid vulnerability (Zubin and Spring 1977). These aspects of the illness are similar to other major medical illnesses, such as asthma and hypertension, and are critical to

early intervention and prevention of psychotic relapses.

Psychotherapeutic Approaches

Psychoanalytic Treatments

Insight-oriented psychotherapies, which are based on the view that symptoms of schizophrenia resulted from psychological conflicts and pathological defense mechanisms, were mainly used in the treatment of psychotic disorders before the 1960s. The few controlled studies during the 1970s, however, showed that although modest benefits were seen with insight-oriented treatments in some domains (ego functioning, cognition), no superior efficacy was seen compared with supportive, reality-oriented treatments such as reality-adaptive therapy (Gunderson et al. 1984). Thus, there is no strong evidence currently for the use of psychodynamic psychotherapy when treating persons with schizophrenia (Malmberg and Fenton 2001).

Major Role Therapy

One of the first systematically studied psychosocial interventions for schizophrenia was major role therapy (MRT), which constituted an early form of social casework and case management for individuals being discharged from the psychiatric hospital. The targets of this treatment were the often-observed challenges patients had in fulfilling major life roles once they were discharged to the community, such as completing school, finding and maintaining competitive employment, and living independently. MRT attempted an atheoretical solution to this problem by providing patients, once they returned to the community, with a social worker and vocational specialist, both of whom would be responsible for brokering resources needed for patients to live independently and meet the demands of adult life.

The efficacy of MRT was tested in a uniquely powerful study that examined the effects of this psychosocial intervention in combination with antipsychotic treatment or placebo, which gave investigators the ability to tease apart the specific effects of medication and psychosocial treatment in the aftercare of patients with schizophrenia (Hogarty et al. 1974). Results not surprisingly revealed that combined MRT and antipsychotic treatment had the greatest impact on patients' functional outcome. What was surprising was the observation that when MRT was provided without medications, patients adjusted to living in the community worse than those receiving no medication or MRT at all. This finding not only demonstrated the benefits of providing psychosocial treatment with pharmacological treatment, but also underscored the important fact that antipsychotic treatment is the foundation upon which psychotherapies must build to provide the most optimal outcome for the patient.

Supportive Therapy

Supportive therapy involves an assortment of strategies that address the concerns raised by the person's plight of having to cope with a serious illness, and the problems of living that may be resulting from the illness. The steps may include offering reassurance, guidance, explanations, and clarifications, and tend not to focus on specific symptoms or the underlying cognitive or emotional impairments. Several studies suggest the possible effectiveness of this approach as compared with treatment as usual (Dickerson and Lehman 2011).

Assertive Community Treatment

The observation that patients leaving the long-term state hospital system in the United States faired quite poorly in the community, which led the development of MRT, also spurred the development of assertive community treatment (ACT; Stein and Test 1980), an even more comprehensive approach to resource brokering and linkage. The proposal of ACT was a simple one, that of creating a "hospital without walls." An interdisciplinary team of mental health professionals (e.g., psychiatrist, nurse, social worker) was to provide the same intensive care to a small number of patients living in the community as these individuals would have received in the hospital, in an effort to help integrate individuals into community life and reduce the burden of maintaining a large state hospital system. The results of the initial study demonstrated considerable benefits to community tenure and reductions in rehospitalization (Stein and Test 1980); although costly, ACT was found to be cost-effective (Weisbrod et al. 1980).

The positive findings were largely confirmed in meta-analytic studies, making ACT one of the most effective first-generation psychosocial treatments for patients with schizophrenia (Burns and Santos 1995; Coldwell and Bender 2007). The intensive program of ACT and MRT spurred the development of less intensive forms of case management in schizophrenia, which have been successful at helping connect patients to needed resources, but their effectiveness on community tenure has been mixed and they have often been observed to be less effective than ACT (Ziguras and Stuart 2000).

Psychoeducation and Coping-Oriented Interventions

Psychoeducational interventions involve 1) providing information about the disorder, mediations, and treatment adherence to patients and their family members and 2) helping individuals to cope with illness-related stresses by using various stress management approaches. Some psychoeducation treatments are focused primarily on the patient, whereas others are family based and focus on supporting the patient and family systems in adjusting to schizophrenia and coping with its effects. The first family psychoeducation intervention for patients with schizophrenia, developed by Hogarty et al. (1986), proved to be remarkably effective in a time when many clinicians were reluctant to give the "bad news" of a schizophrenia diagnosis to the family. Since then, an extensive body of literature has accumulated regarding the efficacy of these interventions, particularly family psychoeducation. Meta-analyses indicate that these interventions reduce high expressed emotion among relatives and greatly decrease patient relapse and rehospitalization rates (Pitschel-Walz et al. 2001). A particularly popular approach is the *multiple-family psychoeducation group intervention* (McFarlane et al. 1995), which offers an expanded social network and thereby confers a margin of protection against relapse. Comparatively fewer studies have examined solely patient-focused psychoeducation, and some evidence does suggest benefits in terms of knowledge about the illness, symptomatology, and functioning (Rummel-Kluge and Kissling 2008). However, benefits appear to be greater when implemented with both the patient and the family (Lincoln et al. 2007).

Social Skills Training

Social skills training (SST) is an early second-generation approach for schizophrenia that uses behaviorist theory and principles to improve social competence of individuals attempting to adjust to community life. Schizophrenia patients manifest deficits in social competence, which is a key factor in outcome and an important target of therapeutic interventions. The goal of SST is to improve day-to-day living skills impacting social functioning and quality of life; SST focuses on components of social competence such as self-care, basic interpersonal and vocational skills, and recreation. These skills are practiced mostly in group settings using techniques based on operant and social learning theory. Historically, token economy was the first such intervention that sought to improve the social behavior of patients with psychiatric illness. Although effective, the results were not generalizable beyond the therapeutic setting. During the 1980s and 1990s, training approaches were developed, notably those by Liberman et al. (1985), to address problems particularly relevant to schizophrenia, such as conversation and community reentry skills. A meta-analysis of randomized controlled trials of SST in schizophrenia showed a large effect size for improvement in skills, a moderate effect size for performance-based social and community skills and for community functioning, and a small effect size for symptoms and relapse (Kurtz and Mueser 2008). More data are needed about predictors of response to SST in schizophrenia and the durability of therapeutic benefits, and evidence suggests some difficulty generalizing skills learned in SST to new environments (Heinssen et al. 2000). Combined treatment with cognitive remediation and SST may be a promising avenue for future research.

Cognitive-Behavioral Therapy

A considerable number of patients with schizophrenia continue to suffer from persistent psychotic symptoms despite pharmacotherapy. Cognitive-behavioral therapies have emerged to address this need. These approaches are based on the assumption that psychotic symptoms such as delusions and hallucinations stem from misinterpretations and irrational attributions caused by impaired social cognition or self-monitoring deficits. Cognitive-behavioral therapy (CBT) seeks to help the patient to rationally appraise the experience of disease symptoms and responses to them, and thereby reduce symptoms, prevent relapse, and improve outcome.

CBT has been found to be effective in meta-analyses focusing on positive symptoms (Zimmermann et al. 2005). Another meta-analysis of CBT showed that the intervention was effective in treating general psychopathology and positive symptoms (Wykes et al. 2008). CBT has also been reported to reduce positive symptomatology and the transition to psychosis in patients with prodromal features of schizophrenia (Morrison et al. 2004). A recent development is the successful application of CBT to negative symptoms, based on the model that defeatist beliefs and negative expectancies might interact to cause negative symptoms in this illness (Grant et al. 2012). Limitations of CBT include the equivocal effects on quality of life, global and social functioning, and relapse prevention; benefits that are usually clearer only in acute psychotic states; and difficulties with implementation.

Disorder-Relevant Illness Management Approaches

The chronic nature of schizophrenia presents the need not only for interventions to manage the acute symptoms of the disorder or even persistent positive symptoms, but also for long-term approaches that can help individuals detect early warning signs of becoming ill and prevent recurrent psychotic episodes. Several disorder-specific interventions have been developed to specifically provide individuals who have schizophrenia with a framework to learn and practice ongoing methods of managing the condition. Some approaches have been long term and highly phase specific, such as personal therapy (Hogarty 2002), which consists of teaching patients stress management and emotion regulation skills to detect and address psychotic prodromes. The treatment is phase specific in that individuals in the early stage of their recovery are taught a basic set of skills for stress management (e.g., conflict avoidance), and as they progress throughout the intervention, they learn more advanced methods (e.g., diaphragmatic breathing, responding to criticism). Three-year trials of personal therapy demonstrated significantly greater reductions in relapse among patients living with family, although individuals not living with family experienced a greater number of psychotic relapses in personal therapy compared with a supportive therapy control, suggesting that although effective, the treatment should be applied only after other critical resources (e.g., housing) have been firmly established (Hogarty et al. 1997).

Other illness management approaches have also been developed, including WRAP (Wellness Recovery Action Planning; Cook et al. 2009) and Illness Management and Recovery (Mueser et al. 2006). Most of these approaches focus on helping patients learn to identify what facilitates their recovery and how to prevent them from becoming psychotic. Reviews of this literature have generally indicated that illness management approaches are helpful at improving medication adherence, reducing psychotic relapses, and reducing symptomatology (Mueser et al. 2002).

Cognitive Remediation

A substantive proportion of schizophrenia patients have impairments in cognition across broad domains of psychomotor speed, attention, working memory and executive function, verbal learning, and social cognition. These deficits are robust (~1 SD), persist during the illness, and have been shown to be some of the strongest predictors of functional outcome (Green 1996). Several cognitive remediation approaches developed over the past two decades involve either compensatory strategies (strategies to organize information, or other environmental aids such as reminders and prompts) or enhancement approaches based on learning techniques. Compensatory interventions, such as Cognitive Adaptation Training (Velligan et al. 2000), have been shown to produce significant improvements in medication adherence and social functioning, as well as reductions in psychiatric relapse in schizophrenia. A greater focus has been on cognitive remediation interventions that are designed to enhance or restore cognition in schizophrenia, and many different approaches have been developed, which have been broadly classified as drill-and-practice or strategic methods of intervention. Drill-and-practice approaches focus on repeating a cognitive exercise until a level

of proficiency is reached. Strategic approaches focus not only on practicing exercises to enhance cognition but also on developing strategies to become more cognitively efficient (e.g., encoding information in meaningful ways, using mnemonic devices).

Meta-analytic reviews of more than 1,000 patients with schizophrenia indicate that cognitive remediation interventions can indeed enhance cognition in schizophrenia, with some generalizable benefits to symptomatology and functioning. However, overall benefits to functional outcome have been largely restricted to those treatments that make use of either strategic training or integrate the treatment of cognition with other psychosocial interventions (e.g., supported employment) (McGurk et al. 2007; Wykes et al. 2011). Studies have also begun to demonstrate the efficacy of these approaches on core neurobiological processes in schizophrenia that contribute to social and nonsocial cognitive impairment in the disorder (e.g., Eack et al. 2010). The recent expansion in understanding of the cognitive underpinnings of this illness and their basis in abnormal neurodevelopment, the growing acknowledgment of the benefits of social-cognitive interventions (Kurtz and Richardson 2012), and the increasing availability of sophisticated computer-based interventions rooted in our growing understanding of neuroplasticity make this field promising. However, many questions about durability and optimal approaches remain regarding cognitive remediation.

Metacognitive and Mindfulness-Based Therapies

Two young and related fields of intervention research in schizophrenia have been shown to have potential benefits to important patient outcomes. *Metacognition* refers to the ability to understand one's own cognitive capacity, strengths, and limitations, and metacognitive therapies have begun to address how accurate reflection on these characteristics can help patients with schizophrenia adjust to their condition and address psychotic symptoms. The focus of metacognitive training is to help individuals become aware of cognitive biases (e.g., jumping to conclusions) that are the basis for delusions and teach methods to correct these biases. These interventions are similar to CBT, both in their aims and in some of their methods, but generally have a greater focus on social cognition and basic cognitive processes. Whereas CBT focuses on "what" a person thinks, metacognitive therapies target "how" a person thinks. Preliminary research has shown that metacognitive training reduces distress associated with delusions and has some benefits on verbal memory and satisfaction with interpersonal relations (Moritz et al. 2011). Although studies are limited, the targeting of metacognition in schizophrenia shows significant promise for advancing the psychosocial treatment of this disorder.

Another set of interventions that also focus on awareness and are increasingly being applied to individuals with schizophrenia are mindfulness-based therapies (Dickerson and Lehman 2011). The focus of some of these approaches is on reducing perseverative thinking about negative and stressful events by allowing such events to come into clear focus, accepting them in a nonjudgmental manner, and then letting the experiences and thoughts pass naturally (Chadwick et al. 2005). Mindfulness meditation can be used as a method of redirecting attention to positive emotions toward the self and others, and might prove to be useful for

addressing some of the negative symptoms of schizophrenia (Johnson et al. 2009). One approach, Acceptance and Commitment Therapy, helps the individual through meditation and related exercises to experience and accept symptoms such as psychosis mindfully and nonjudgmentally. Overall, as for metacognitive training, the evidence base for mindfulness-based therapies in schizophrenia is small, with at least one study demonstrating quantitative benefits to subjective well-being (Chadwick et al. 2005). Although the rationale for the potential benefits of mindfulness-based therapies in schizophrenia is compelling, particularly when placed in the context of the large body of evidence supporting their efficacy in other health conditions, more research is needed to continue the development of these interventions and assess their value to patient outcomes.

Supported Employment

As treatments were developed to help address social skills problems, persistent symptoms, and long-term community adjustment in patients with schizophrenia, the opportunities for patients and their clinicians to work toward reengaging in major functional activities became even greater. For many patients, a key activity to be resumed is work, and supported employment interventions were developed to help facilitate the ability of patients to engage in competitive work.

A variety of supported employment models have been developed for patients with schizophrenia, with the most commonly studied being Individual Placement and Support (IPS; Bond 1998). The principles of IPS consist primarily of rapid job placement, job counseling and support, disability benefits management, and an emphasis on competitive employment. In most implementations of IPS, patients who are interested in work will see a supported employment specialist who will help them identify potential jobs, help them obtain those jobs (e.g., practice interviewing), and then work with the patients in the job to identify ways to accommodate their condition and support vocational success. An important principle of the IPS model is that only minimal prevocational training is provided so that the job itself becomes the primary training environment. This approach was selected, in part, because many patients were relegated to long-term prevocational training with little opportunity to ever practice their skills in the workforce.

Meta-analytic reviews of supported employment interventions for patients with schizophrenia have shown medium to large effects on increasing employment and total hours worked (Twamley et al. 2003), with some studies reporting long-term maintenance of these effects over the course of a decade (Becker et al. 2007).

Conclusion

In summary, research on psychosocial approaches to the treatment of schizophrenia has yielded incremental evidence of the efficacy of CBT, SST, family psychoeducation, and cognitive remediation. In general, little evidence supports the efficacy of psychodynamic therapies in schizophrenia, and in fact some evidence indicates potential harm (Mueser and Berenbaum 1990). There is evidence that Individual Placement and Support is more effective than traditional approaches to vocational rehabilitation in helping patients to find and maintain competitive employment. Other psychotherapeutic approaches, such as compli-

ance therapy based on motivational interviewing principles to improve adherence, have yet to yield systematic evidence in support of their efficacy (McIntosh et al. 2006).

It is important for the clinician to keep in mind that treating a patient with chronic psychosis, as with any other illness, is as much an art as a science. Several broad principles might underlie efforts to maximize benefits from psychotherapy. First, the role of a positive and continuous *therapeutic alliance* as a predictor of therapeutic outcome cannot be emphasized enough (Frank and Gunderson 1990). Second, it is important to *integrate the pharmacological and psychotherapeutic approaches,* preferably by the same treatment team. Third, it is worth considering judiciously selecting psychotherapeutic strategies; treatment approaches that *synergistically combine* several modalities of intervention, such as personal therapy (Hogarty 2002) and cognitive remediation along with supportive employment (McGurk et al. 2007), tend to have more robust effects. Fourth, as discussed earlier, psychotherapeutic strategies need to be appropriately *tailored to the phase of the illness* in which the patient is presenting, because the primary goals of intervention might vary across phases (see Table 10–3). Thus, although CBT and supportive therapy might be most relevant for the psychotic phase, supportive employment, cognitive remediation, and SST might be the main focus during the recovery, chronic, and more stable phases. Finally, given the heterogeneity of the clinical manifestations of schizophrenia, it is important to choose the *right treatment for the right patient;* whereas supportive treatment might benefit all symptom domains, CBT may be particularly beneficial for patients with residual psychotic symptoms, cognitive remediation and SST for those with cognitive and/or social cognition deficits, and ACT for those at risk for frequent hospitalizations or those have had recent homelessness.

More research is needed to examine those active ingredients of the therapeutic modalities that work and to identify the synergistic effects of combinations of interventions that are hypothesis driven and cost-effective. Relatively few rigorously conducted trials of psychosocial interventions have been reported in the early course of schizophrenia, a phase of the illness when effective interventions are likely to yield long-term outcome benefits.

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CHAPTER 11

Pharmacological Treatment of Psychosis

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Psychotic symptoms may be the primary characteristic of a specific disorder such as schizophrenia, occur secondary to a mood disorder such as major depression, or be due to a known causative factor such as a drug-induced paranoid reaction. Schizophrenia is the best studied disorder in terms of pharmacological treatment, and schizoaffective disorder is often included in these medication trials. Although antipsychotics have often been prescribed for major mood disorders with psychotic features, the U.S. Food and Drug Administration (FDA) has dramatically expanded their approved uses in recent years. Several of these agents are now indicated for bipolar and unipolar disorders, even in the absence of psychosis. Antipsychotics are also often prescribed off-label, but limited data are available to guide their appropriate use. For example, they are widely administered to older patients experiencing behavioral disturbances or psychosis associated with dementia. The potential risks of such off-label use are underscored by an FDA-mandated box warning for all antipsychotics, primarily due to an increased incidence of cardiovascular events and the related morbidity and mortality.

Because individuals with schizophrenia may experience subtle changes in behavior and cognition for long periods prior to their first acute psychotic episode, early diagnosis and intervention are increasingly emphasized. Recognition of impending or subtle signs of psychosis and introduction of an antipsychotic to reduce duration of untreated symptoms may have a substantial impact on long-term outcome. For example, a recent meta-analysis found that limiting the duration of untreated psychosis to less than 9 months was associated with a substantially greater reduction in negative symptoms (Boonstra et al. 2012). Imaging studies indicate that during the early years after illness onset, a subset of patients with schizophrenia may demonstrate significant decreases in gray matter and white matter, as well as increases in cere-

brospinal fluid (Andreasen et al. 2011). The use of antipsychotic drugs in this population, however, is complicated by conflicting reports of an association between exposure to them and either neuroprotective or neurotoxic effects (Lewis 2011).

Although antipsychotic drug therapy is used for several FDA-approved and unapproved indications, the existing evidence base for these medications is strongest for their role in managing multiple-episode schizophrenia, which is the focus of this chapter. (For management of first-episode patients, see Chapter 8, "Early-Stage Schizophrenia.") In this chapter, data for both acute and long-term management are considered. Because inadequate response and treatment resistance are common in this population, strategies to augment standard antipsychotics or to serve as alternatives are also reviewed. Throughout the chapter, an emphasis is placed on the value of a risk-benefit assessment that takes into account the substantial safety and tolerability issues associated with this class of psychotropic medications.

Choice of Antipsychotic

The choice of an initial antipsychotic is often determined empirically, taking into account the quality and quantity of the extant evidence base, as well as the duration of clinical experience with a specific agent and its relative risk-benefit ratio (Janicak et al. 2011). The results from large "pragmatic trials" and expert consensus guidelines have helped to better inform clinicians about their choice of antipsychotic (e.g., Kreybuhl et al. 2010; Lieberman et al. 2005). Determining factors may include personal preference, prior history of response, history of treatment resistance, proclivity to certain adverse effects, presence of comorbid substance use and/or medical disorders, available formulations, long-term planning, and cost. Given the present state of knowledge about the relative efficacy of the various first- and second-generation agents, the choice of an antipsychotic is often based as much on safety and tolerability as on efficacy.

The use of biological markers to facilitate this process, however, is rapidly developing. For example, pharmacogenetics and pharmacogenomics should increasingly clarify how inheritance and acquired genetic variations impact a drug's effectiveness or adverse-effect profile (Lotrich 2012). This growing evidence base promises to facilitate identification of biomarkers to help with choice of drug, duration of treatment, and/or dosage for specific individuals; avoidance of treatments likely to produce adverse effects in specific individuals; improvement in the understanding of a drug's mechanism of action; improvements in medication adherence; and reduction in relapse rates (Wang et al. 2011). *Pharmacogenetics* focuses on a candidate gene using single-nucleotide polymorphisms (SNPs) associated with a drug's action and tested for an association to clinical response. For example, this approach has included studies on serotonin transporter gene polymorphisms as they relate to the effects of clozapine (Kohlrausch et al. 2010). *Pharmacogenomics* involves genome-wide association studies, which use microarray technology to interrogate thousands of SNPs randomly distributed across the genome. In this context, multigene approaches may help identify "profiles" of SNPs with additive predictive value in terms of clinical effect. For example, as part of iloperidone's development, six gene loci were identified that may be associated with response to the drug (Lavedan et al. 2009).

Presently, 27 agents are available in the United States that can be grouped into typical or first-generation antipsychotics (FGAs) and atypical or second-generation antipsychotics (SGAs). Although there is debate about the validity of such a distinction, given the many similarities between drugs within these two groups, most experts agree that differences in adverse effects can often help to distinguish them. Thus, neuromotor toxicity is more characteristic of high-potency FGAs (e.g., haloperidol, fluphenazine, thiothixene), whereas weight gain and metabolic dysregulation are more characteristic of certain SGAs (e.g., clozapine, olanzapine, quetiapine).

Table 11–1 lists the 27 FGAs and SGAs available in the United States and includes information about the recommended dosing range for their oral formulations, as well as for alternative routes of administration.

Acute Treatment of Psychosis

For patients with a history of recurrent psychotic episodes who have been responsive to prior treatment, a common strategy for acute exacerbations is to start with a previously effective agent or a generic SGA, such as risperidone or olanzapine. These latter agents have alternative formulations (e.g., acute parenteral, oral liquid, disintegrating tablets), which may be useful for patients in more emergent situations, patients who are not cooperative with standard oral preparations, or patients who cannot swallow tablets or capsules. Both risperidone and olanzapine also have long-acting injectable (LAI) formulations, which can make a transition from the oral preparation easier if such a maintenance strategy is appropriate. An alternative or subsequent strategy is to begin with a moderate- or high-potency FGA, such as perphenazine or haloperidol. For more agitated and disruptive behaviors unresponsive to de-escalation techniques, the short-term use of a benzodiazepine (e.g., oral or acute parenteral lorazepam) may facilitate calming the patient while minimizing the dose of antipsychotic required. Concerns about the high comorbidity with substance use disorders in this population, however, may require alternative strategies. In this context, acute parenteral FGAs and SGAs, as well as acute loxapine inhalation therapy, are also available (Allen et al. 2011). The overall goal is to maximize the intended antipsychotic effect with the minimally effective dose and to minimize longer-term exposure to polypharmacy. This is particularly true for extended exposure to benzodiazepines, which may increase mortality rates (Tiihonen et al. 2012). In addition to substantially reducing adverse effects (e.g., acute extrapyramidal side effects [EPS]), this approach facilitates adherence to longer-term treatment. Although it may take several weeks to optimize acute response, most patients should demonstrate acceptable improvement during the first 2 weeks. If not, clinicians should consider an alternate agent or augmentation of the initial treatment. The latter may involve additional medications (e.g., combined antipsychotics), alternative biological therapies (e.g., therapeutic neuromodulation), psychotherapeutic interventions (e.g., cognitive remediation), and/or psychosocial approaches (e.g., social skills training).

In patients who experience two or more failed adequate antipsychotic trials, clozapine should be considered (Buchanan et al. 2010). This agent has multiple advantages over other presently available antipsychotics, including evidence for

TABLE 11–1. First- and second-generation antipsychotics

Name	Oral dosing range (mg/day)	Alternative formulations
Phenothiazines		
Aliphatics		
Chlorpromazine	100–1,000	Acute parenteral; rectal suppository
Promazine	25–1,000	
Triflupromazine	20–150	
Piperidines		
Thioridazine	30–800	Oral concentrate; oral suspension
Mesoridazine	20–200	
Piperacetazine	20–160	
Piperazines		
Fluphenazine	5–40	Oral concentrate; acute parenteral; long-acting injectable (12.5–25 mg/2–3 weeks)
Trifluoperazine	2–60	
Perphenazine	2–60	
Acetophenazine	40–80	
Prochlorperazine	15–125	
Thioxanthenes		
Thiothixene	6–60	
Chlorprothixene	10–600	
Dibenzoxazepine		
Loxapine	20–250	Acute inhalant (single dose of 5 or 10 mg)
Butyrophenones		
Haloperidol	3–50	Oral concentrate; acute parenteral; long-acting injectable (50–200 mg/4 weeks)
Droperidol	1.25–2.5	IV or IM parenteral only
Dihydroindolone		
Molindone	15–225	Oral concentrate
Dibenzodiazepine		
Clozapine	100–900	Oral rapid dissolving
Benzisoxazoles		
Risperidone	2–8	Oral liquid; rapid dissolving; long-acting injectable (150–405 mg/2–4 weeks)
Paliperidone	3–12	Oral extended release; long-acting injectable (117 mg/4 weeks)
Iloperidone	12–24	
Lurasidone	40–80	

TABLE 11–1. First- and second-generation antipsychotics *(continued)*

Name	Oral dosing range (mg/day)	Alternative formulations
Thienobenzodiazepine		
Olanzapine	5–20	Oral rapid dissolving; acute parenteral; long-acting injectable (150–405 mg/2–4 weeks)
Dibenzothiazepine		
Quetiapine	75–800	Oral immediate and extended release
Benzisothiazolyl		
Ziprasidone	40–160	Acute parenteral available
Quinolinone		
Aripiprazole	5–30	Oral liquid; oral rapid dissolving; acute parenteral; long-acting injectable (400 mg/4 weeks) available
Dibenzo-oxepino pyrrole		
Asenapine	10–20	Sublingual only

benefit in treatment-refractory, hostile, aggressive, violent, and suicidal patients, as well as an associated lower risk of death (Table 11–2). In addition, blood levels can guide optimization of dosing (e.g., ≥350 ng/mL). Unfortunately, this drug also carries several disadvantages requiring a careful risk-benefit assessment prior to its prescription. Ongoing blood count monitoring is important to reduce the incidence and consequences of neutropenia and agranulocytosis, which add to the cost and complexity of managing patients.

Maintenance Treatment of Psychosis

Given the recurrent nature of schizophrenia, long-term, continuous treatment is appropriate for most patients. The value of persisting with therapy at doses effective to control acute positive symptoms is underscored by the results of a meta-analysis that found active drug significantly more effective than placebo in preventing relapse for up to 12 months (Leucht et al. 2012). Another meta-analysis showed a modest superiority (i.e., number needed to treat [NNT]=17) for SGAs over FGAs in preventing relapse (Kishimoto et al. 2013). As the authors noted, however, these results must be considered in the context of drug-related, long-term morbidity and mortality, as well as their impact on social outcomes. In this context, evidence indicates that SGAs may have a clinically relevant superiority over FGAs in terms of subjective sense of well-being (Lambert et al. 2011).

One of the most difficult aspects of treating psychosis is devising a strategy to help patients adhere to their medications over prolonged time frames. This difficulty underscores the need to develop an effective alliance to increase the

TABLE 11–2. Clozapine: potential advantages and disadvantages

Advantages	Disadvantages
May benefit treatment-refractory patients	*Box warnings*
May reduce suicidal, aggressive, or violent behavior	Agranulocytosis
	Seizures
May increase life expectancy	Myocarditis
Has diminished extrapyramidal side effects	Orthostasis
Minimizes risk for or improves tardive dyskinesia	Increased mortality in dementia
Avoids hyperprolactinemia	*Other adverse effects*
	Weight gain/metabolic syndrome
	Diabetic ketoacidosis
	Gastrointestinal hypomotility
	Sialorrhea

chances of adequate adherence. In part, clinicians must emphasize that taking medication is not the primary goal but is an important means to help patients achieve a better quality of life (Weiden et al. 2012). LAI antipsychotics may play an important role by improving adherence, more easily identifying nonadherence, and decreasing relapse rates (Kane et al. 2012).

Management of Treatment Resistance

Given the multiple domains that characterize schizophrenia, it is increasingly evident that drugs acting primarily through dopaminergic mechanisms do not adequately address the entire spectrum of symptoms. Although existing agents are relatively effective for positive symptoms, they are far less effective for primary persistent negative, neurocognitive, and mood symptoms. Furthermore, safety and tolerability issues often preclude an effective ongoing course of standard treatment. As a result, initiatives to improve outcomes include refinements in existing agents to enhance efficacy and/or to decrease adverse effects, the development of drugs with alternative mechanisms of action, and the use of agents to augment standard antipsychotics. Although many more potential approaches are considered in the literature, those selected in this chapter for discussion as alternatives to or augmentation of available antipsychotics are based primarily on promising data from controlled trials. It should be noted, however, that the quality and quantity of evidence to support these strategies is presently limited and often in the form of pilot study data.

Polypharmacy

Combining antipsychotics is a frequently employed clinical strategy. One explanation to support this approach is the ability to augment the effects of the first agent by "personalizing" the neuroreceptor profile for a given patient. The most frequent combination studied to date involves the addition of risperidone to clozapine in patients who have an insufficient response to clozapine monotherapy. Results

from most of these randomized controlled trials (RCTs), however, are negative. Furthermore, a meta-analysis of controlled trials comparing various antipsychotic combinations versus monotherapy did not produce firm recommendations about the value of polypharmacy (Correll et al. 2009). Of note, there are substantial disadvantages to polypharmacy, as outlined in Table 11–3.

TABLE 11–3. Antipsychotic polypharmacy: potential advantages and disadvantages

Advantages	Disadvantages
Eases transition from one agent to another	Inadequate data to support augmentation effect
Supplements long-acting agents during initiation or exacerbation	Increased risk for adverse effects (e.g., anticholinergic; QTc prolongation)
Improves specific symptoms (e.g., quetiapine for dyssomnia or anxiety)	Increased risk for drug interactions
Need to use lower doses of two agents due to safety or tolerability issues with standard doses of a single agent	Adherence problems
Augments efficacy of first antipsychotic	Increased cost

Neurotransmitters

Dopamine

All available antipsychotics directly impact the dopamine system. Given the inadequate response in many patients, as well as safety or tolerability issues, alternative means of modulating the dopamine system (e.g., D_1–D_5 receptors) are being considered. For example, dopamine D_1 receptors are abundant in the prefrontal cortex and play an important role in cognition (e.g., working memory). To date, attempts to modulate their activity, however, have not clearly improved these deficits. Cariprazine is a partial agonist at the D_2/D_3 and serotonin 5-HT_{1A} receptors. Preclinical models predict procognitive effects, and on the basis of positive Phase II results, Phase III trials are ongoing. Studies are also being conducted with D_3 receptor antagonists; however, D_4 receptor antagonists have not proven beneficial thus far.

Norepinephrine

Norepinephrine increases dopamine output in the medial prefrontal cortex. Clinically, this may translate to improved vigilance, cognition, and mood, as well as moderation of stress reactions. Blockade of reuptake transporters, antagonism of presynaptic α_2 norepinephrine receptors (preventing autoreceptor negative feedback on activity), and agonism of postsynaptic α_2 norepinephrine receptors are possible therapeutic approaches. To date, however, RCTs have generated mixed results regarding cognitive benefit for norepinephrine reuptake inhibitors (e.g., reboxetine or atomoxetine) as add-on therapy to antipsychotics.

Serotonin

Given the varied impact of SGAs on the serotonin system, much interest is focused on its numerous receptor subtypes. For example, evidence suggests that 5-HT_{1A}

receptor agonists may enhance the antipsychotic effects of D_2 receptor antagonists, and several compounds possessing these two properties are now being studied. Other receptor subtypes are also potential add-on candidates to improve psychosis, negative symptoms, and certain cognitive domains. They may also reduce the dose of standard antipsychotic required, lessening the adverse effect burden. These include selective 5-HT_{2A} inverse agonists (e.g., pimavanserin), selective 5-HT_{2A} antagonists, selective 5-HT_{2C} agonists (e.g., vabicaserin), 5-HT_3 antagonists (e.g., ondansetron), 5-HT_4 receptor agonists, and 5-HT_6 (e.g., latrepirdine) and 5-HT_7 antagonists (see, e.g., Meltzer et al. 2012). Of note, the most recent SGAs, iloperidone, asenapine, and lurasidone—all demonstrate several of these properties, including blockade of 5-HT_6 and 5-HT_7 receptors.

Glutamate

Glutamate is the primary excitatory neurotransmitter and one of the most abundant free amino acids in the central nervous system (CNS). It contributes to the formation, maintenance, and plasticity of synaptic function and plays a role in sensory processing, memory, and executive functioning (Konradi and Heckers 2003). In schizophrenia, abnormal glutamate-regulated activity can adversely impact neuroplasticity and cause neuronal toxicity. In particular, the glutamate *N*-methyl-D-aspartate (NMDA) ionotropic receptor may be dysfunctional (Moghaddam and Javitt 2012). Although drugs that block this receptor (e.g., phencyclidine, ketamine) can produce a psychotic syndrome closely resembling schizophrenia, Moghaddam and Javitt (2012) opine that it is the resultant overactivity of glutamate at other sites (particularly the α-amino-3-hydroxy-5-methyl-4-isoxazle propionic acid [AMPA] ionotropic receptor) that may produce or worsen psychosis. Group II metabotropic glutamate (mGlu) 2/3 presynaptic receptors are also implicated in the pathophysiology of schizophrenia and may be potential therapeutic targets. Finally, glutamate has reciprocal interactions with other relevant neurotransmitter systems (e.g., dopamine, γ-aminobutyric acid [GABA], acetylcholine), all of which are modulated indirectly by impacting glutamate activity. Given these lines of evidence and the substantial shortcomings of existing drug therapies, there is great interest in developing a "glutamatergic strategy" to treat various aspects of schizophrenia, particularly negative and neurocognitive symptoms. Although direct impact on various glutamate receptors may produce neuronal excitotoxicity and damage, various indirect approaches may prove to be less risky but still therapeutic.

The facilitation of glycine whose site is co-located with the glutamate site on the NMDA ionotropic receptor can improve the efficiency of this receptor's channel (Konradi and Heckers 2003). In this context, a meta-analysis reported that glycine improved positive and total symptoms of schizophrenia when used as an adjunct with non-clozapine antipsychotics, but worsened symptoms when combined with clozapine (Singh and Singh 2011). The Cognitive and Negative Symptoms in Schizophrenia Trial, however, did not find benefit for add-on glycine or D-cycloserine (a selective partial NMDA receptor agonist) when compared with placebo for the treatment of negative symptoms or cognitive impairment (Buchanan et al. 2007). A more recent placebo-controlled trial also did not find benefit for low-dose adjunctive D-serine (a naturally occurring allosteric modulator of the NMDA receptor) in treating negative and cognitive symptoms (Weiser et al. 2012). To circumvent the relatively poor CNS

penetration and need for high doses of these amino acids, another approach is to administer agents that act as glycine transport inhibitors, a strategy similar to the use of selective serotonin reuptake inhibitors (SSRIs) for depression. In this context, a 6-week, double-blind trial found that adjunctive sarcosine (*N*-methylglycine) (2 g), but not D-serine, was superior to placebo based on several clinical outcome measures (Lane et al. 2010).

Another strategy is to target the mGlu2/3 presynaptic receptors, whose stimulation inhibits further glutamate release. In this context, pomaglumetad methionil (an mGlu2/3 receptor agonist) demonstrated antipsychotic effects significantly better than placebo and similar to olanzapine in a Phase II controlled study. Subsequent trials, however, failed to demonstrate efficacy for this agent compared with placebo, leading Eli Lilly to suspend Phase III development of this agent (Kinon and Gomez 2013; Kinon and Gomez 2011).

Alternative approaches include the use of adjunctive *N*-acetyl cysteine (NAC), which stimulates Glu receptors indirectly by enhancing formation of glutathione, a neuroprotective free radical scavenger that moderates oxidative stress. One placebo-controlled, 24-week trial supported the benefits of add-on NAC (1 g bid) in 140 patients with chronic schizophrenia (Berk et al. 2008). Other strategies involved adjunctive anticonvulsants such as lamotrigine (an inhibitor of glutamate release) plus clozapine; memantine (a weak nonselective NMDA receptor antagonist) plus clozapine; and AMPA-receptor modulators (e.g., ampakines such as CX516 and minocycline). Although preliminary data from controlled trials are available to support each of these approaches, design limitations and difficulty with or lack of replication leave unclear their potential benefit (de Lucena et al. 2009; Goff et al. 2001; Levkovitz et al. 2010; Tiihonen et al. 2009).

γ-Aminobutyric Acid

GABA is the primary inhibitory neurotransmitter in the CNS. Several lines of evidence indicate that cortical and subcortical GABA activity is disrupted in schizophrenia. Preclinical and clinical evidence also supports a potential role for GABA agonists to improve various symptoms. For example, activation of GABA interneurons can decrease hyperactivity of mesolimbic dopamine and/or glutamate, thereby reducing positive symptoms. Conversely, activation may also compensate for hypoactivity of prefrontal cortical dopamine, thereby improving negative symptoms and cognitive deficits.

Various strategies are employed to modulate the GABA system as a therapeutic approach to schizophrenia. One involves the use of anticonvulsants that work in part through GABAergic mechanisms (e.g., divalproex sodium). Following an initial 4-week study that had encouraging results, a large 12-week, controlled trial did not demonstrate efficacy for divalproex sodium when that agent was used as an adjunct to olanzapine or risperidone (Casey et al. 2009). Divalproex sodium did, however, control hostility and anxiety more effectively than placebo.

Another approach is the use of selective agonists of $GABA_A$ receptors. Working memory deficits are associated with impairments in prefrontal cortex function. Altered gamma-band oscillations may reflect desynchronization of pyramidal cell activity, which depends in part on $GABA_A$ receptor-mediated neurotransmission (Lewis et al. 2008). A posi-

tive, small (N=15), proof-of-concept, placebo-controlled trial with MK-0777 (a relatively selective agonist of $GABA_A$ receptors containing α_2 subunits) led to a larger (N=60), 4-week, placebo-controlled trial. Although the results of this second study were negative, the authors speculated that a more potent partial agonist with greater intrinsic activity might still improve cognition (Buchanan et al. 2011).

Acetylcholine

The cholinergic system can affect dopamine and glutamate pathways in the CNS and is implicated in sensory processing and cognition, modulated through both its nicotinic and muscarinic receptors. One hypothesis for the heavy smoking patterns seen in patients with schizophrenia is that stimulation of nicotinic receptors may temporarily improve sensory processing. In this context, a 4-week, small (N=31), proof-of-concept, controlled trial found that the adjunctive use of the α_7 nicotinic receptor agonist DMXB-A (75 or 150 mg/day) was significantly better than placebo for negative symptoms (but not cognition) and was generally well tolerated (Freedman et al. 2008). There is also an early signal for potential cognitive benefits with adjunctive $\alpha_4\beta_2$ receptor agonists (e.g., varenicline), but the benefits must be balanced against reports of behavioral toxicity with this specific agent.

Antagonism of muscarinic receptors (M_1–M_5) can adversely impact cognition. A small (N=20), controlled, crossover trial found that monotherapy with xanomeline (75–225 mg/day), a relatively selective M_1/M_4 cholinergic receptor agonist, was significantly more effective than placebo on various measures, including improvement in verbal learning and short- term memory (Shekhar et al. 2008). Although gastrointestinal effects were common with xanomeline, there were no discontinuations due to adverse effects. Selective allosteric activation of M_1 or M_4 receptors will help to clarify whether this potential benefit is due to actions at either site or to their combination. In addition, the question of whether activation of M_2, M_3, or M_5 receptors might also be efficacious is left open.

Histamine

Histamine has four identified receptor subtypes and can modulate arousal and cognitive function. Preclinical and clinical evidence support a potential role for histamine (e.g., H_3 receptor antagonists and inverse agonists) related to the cognitive deficits associated with schizophrenia. One such agent is pitolisant, an H_3 receptor inverse agonist with potential procognitive activity (Schwartz 2011). Further, in a pilot study (N=30), famotidine (an H2 receptor antagonist) was superior to placebo on several symptom measures when added to standard treatment (Meskanen et al. 2013).

Other Approaches

Antidepressants

Although several controlled studies have assessed the adjunctive role of various antidepressants to improve mood, cognition, and negative symptoms, they involved small sample sizes and short durations. The best evidence to date supports a role for mirtazapine in improving various symptoms (Phan and Kreys 2011).

Steroids

The hypothalamic-pituitary axis is implicated in the pathophysiology of and stress vulnerability associated with schizophrenia. In this context, pregnenolone and dehydroepiandrosterone (DHEA) are neurosteroids whose multiple actions predict potential to improve

symptoms of schizophrenia. Thus far, promising preliminary trials demonstrate their benefit as add-on therapies to improve positive, negative, and certain cognitive symptoms, as well as to ameliorate EPS (Marx et al. 2011).

Anti-Inflammatory Agents

Several lines of evidence implicate inflammatory processes (e.g., abnormal levels of cytokines and autoantibodies in serum and cerebrospinal fluid) in the pathophysiology of schizophrenia. A recent meta-analysis concluded that add-on nonsteroidal anti-inflammatory drugs (NSAIDs) could reduce symptom severity, with a specific added benefit for aspirin to possibly reduce cardiac and cancer mortality in the schizophrenia population (Sommer et al. 2012). Another approach is the use of add-on minocycline (a second-generation tetracycline) with anti-inflammatory, antimicrobial, and possible neuroprotective properties through modulation of glutamate-induced excitotoxicity. Results of a longitudinal, placebo-controlled trial supported earlier case reports; open-label and acute controlled trial data demonstrated an augmenting effect when minocycline (200 mg/day) was added to an antipsychotic (Levkovitz et al. 2010).

Cannabinoids

Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive substance in cannabis. Stimulation of central cannabinoid receptors (e.g., CB_1) can produce transient symptoms similar to schizophrenia, and exacerbate preexisting psychosis, and with early exposure may contribute to the risk of developing schizophrenia. Preclinical and clinical data suggest a procognitive effect (e.g., on working memory) with CB_1 antagonists, possibly through modulation of GABA release in the prefrontal cortex (Skosnik et al. 2012).

Hormonal Agents

In women, decreases of estrogen during the postpartum period and menopause appear to increase the risk for a first episode or relapse of schizophrenia. By contrast, increases in estrogen during pregnancy and certain phases of the menstrual cycle appear to improve psychosis and reduce relapse rates. Support for an *estrogen protective hypothesis* also comes from preliminary controlled trial results, primarily with add-on estradiol and possibly the selective estrogen modulator raloxifene (Begemann et al. 2012).

Therapeutic Neuromodulation

Electroconvulsive therapy (ECT) has been used for the short-term treatment of schizophrenia since its introduction in the 1930s and is still a widely applied approach in many parts of the world for this diagnosis. A Cochrane review concluded that ECT plus an antipsychotic may be particularly beneficial when rapid reduction of symptoms is required or when there is insufficient benefit from medication alone (Tharyan and Adams 2005). More recently, preliminary evidence supports a possible role for repetitive transcranial magnetic stimulation (rTMS), particularly for the short-term treatment of refractory auditory hallucinations, negative symptoms, and possibly working memory deficits in schizophrenia (Barr et al. 2013; Dlabac-de Lange et al. 2010; Slotema et al. 2012). Finally, a small (N=30) controlled trial found that transcranial direct-current stimulation was superior to a sham procedure in reducing medication-refractory auditory hallucinations in patients with schizophrenia (Brunelin et al. 2012).

An exciting new development in neuroscience is the field of optogenetics (Deisseroth 2012). This approach employs a fiber optic–generated light/neural interface to increase or decrease neuronal activity. For example, stimulation of parvalbumin neurons can impact the rhythmicity of gamma oscillations, resulting in modulation of neocortical circuitry that is dysregulated in schizophrenia (Lewis et al. 2008; Sohal 2012). Although the potential clinical application of optogenetics will require years of technological refinements, the promise of developing more selective targeted therapies is enormous.

Adverse Effects of Antipsychotics

The overall effectiveness of any treatment is determined by the balance between its efficacy and its safety and tolerability profile. Table 11–4 provides a qualitative overview of the level of risk for complications associated with haloperidol and the available SGAs (Janicak et al. 2011).

Neuromotor Effects

Potent D_2 blockade in the absence of compensatory 5-HT_{2A} blockade produces more severe acute EPS, which may predispose to developing tardive dyskinesia. Haloperidol and other high-potency FGAs are most problematic in this regard, and the SGAs clozapine and quetiapine are least problematic. Although not common, associated laryngeal spasm can be life threatening. When clinically feasible, lowering the dose may be sufficient to manage these symptoms. Antiparkinsonian agents (e.g., benztropine) can reduce these symptoms but are not generally used prophylactically due to their detrimental peripheral and central effects. Alternatively, benzodiazepines may also be effective, but issues of dependence, excessive sedation, and motor incoordination limit their use. Propranolol or benzodiazepines may also be useful for akathisia.

Hyperkinetic, abnormal, involuntary movements characteristic of tardive dyskinesia can occur as a result of more extended drug exposure. Other risk factors include older age, female gender, a mood disorder diagnosis, and CNS compromise. Management includes limiting drug exposure, stopping the antipsychotic (preferably with a slow taper), or switching to an SGA such as quetiapine or clozapine. While the DA-depleting agent tetrabenazine is frequently recommended, expense and adverse effects (e.g., depression, parkinsonism) limit its usefulness. Alternate choices may include amantadine, benzodiazepines, β-blockers, and levetiracetam. Botulinum toxin injections can improve persistent blepharospasm and tongue protrusion. In a patient with refractory, disabling symptoms, resuming a potent D_2 blocking agent (e.g., haloperidol) can temporarily reduce symptoms but may ultimately worsen tardive dyskinesia.

Weight and Metabolic Effects

An important contributor to the shortened life expectancy of patients with schizophrenia is the high prevalence of medical comorbidities. Thus, a critical issue is the adverse weight gain and metabolic effects that are associated with antipsychotics and that heighten the risk of subsequent cardiovascular and cerebrovascular disorders. Although certain SGAs (e.g., clozapine, olanzapine) are usually more problematic in this regard, high-potency FGAs (e.g., haloperidol)

TABLE 11–4. Common adverse effects of haloperidol versus second-generation antipsychotics[a]

Effects	HAL	CLZ	RIS	OLZ	QUE	ZIP	ARP	PAL	ILO	ASN	LUR
Neuromotor	+++	0	++	0/+	0	0/+	++	++	+	0	+
Weight gain/ metabolic	+	+++	++	+++	++	0/+	0/+	++	+	+	0/+
Cardiovascular	++	+++	+	+	+	++	0	++	0/+	0	0/+
Prolactin	++	0/+	+++	0/+	0/+	0/+	0	+++	+	+	+
Cholinergic	0	+++	0/+	+/++	0/+	0/+	0	0/+	0/+	0	0
Hematological	0	+++	0	0	0	0	0	0	0	0	0
Sedation	+	+++	+	+/++	+++	++	+	+	+	+	+

Note. ARP=aripiprazole; ASN=asenapine; CLZ=clozapine; HAL=haloperidol; ILO=iloperidone; LUR=lurasidone; OLZ=olanzapine; PAL = paliperidone; QUE=quetiapine; RIS=risperidone; ZIP=ziprasidone.
0=none; +=mild; ++=moderate; +++=substantial.
[a]At appropriate doses.

and more recent SGAs (e.g., iloperidone, asenapine, lurasidone) appear to be less problematic. It is important to be proactive in educating patients about these risks, encouraging healthier lifestyles, and monitoring from the onset for treatment-related changes consistent with metabolic syndrome (e.g., body mass index, blood pressure, lipids, glucose levels). In addition, there is modest support for some pharmacological (e.g., metformin, topiramate) and behavioral (nutritional counseling combined with exercise) interventions to prevent weight gain and promote weight loss (Das et al. 2012).

Cardiovascular Effects

Patients taking antipsychotics have a greater incidence of sudden cardiac death compared with both nonusers and former users of these agents. According to Ray et al. (2009), the risk is similar for both FGAs and SGAs and appears to increase significantly with increasing dose. The authors opine that these drugs may produce serious ventricular arrhythmias by potassium channel blockade and prolongation of cardiac repolarization. Specific agents with heightened warnings include chlorpromazine, thioridazine, mesoridazine, haloperidol, droperidol, ziprasidone, and paliperidone. Thus, baseline and periodic electrocardiographic monitoring should be considered, especially in patients whose medical status warrants more careful observation. Also, the dose of antipsychotic should be frequently reassessed and maintained at the lowest effective level.

Clinically relevant orthostatic hypotension can occur with many antipsychotics, particularly agents with potent α_1-adrenergic blocking properties. Associated symptoms may include syncope, transient ischemic attacks, stroke, myocardial infarction, and death. Gradual dose titration, blood pressure monitoring, support hose, and educating patients about slowly rising from a supine position may all help to minimize these risks. If symptoms persist, fludrocortisone (0.05–0.2 mg/day) is a reasonable first-line drug therapy.

Clozapine is associated with myocarditis, pericarditis, and cardiomyopathy. When prescribing this agent, clinicians should monitor for possible early signs such as palpitations, chest pain, or dyspnea; be alert for signs of an immune response, such as fever, leukocytosis, or eosinophilia; check for signs of direct injury, such as elevations in creatine phosphokinase, lactate dehydrogenase, or aspartate aminotransferase levels; and, when appropriate, look for signs of cardiac dysfunction based on an electrocardiogram or echocardiogram.

Prolactin Effects

D_2 receptor antagonism in the tuberoinfundibular tract promotes increased release of prolactin. Risperidone, paliperidone, and haloperidol are the most common agents implicated. Although such increases do not necessarily produce clinical symptoms, they can at times cause substantial adverse events. These may include gynecomastia, galactorrhea, sexual dysfunction, infertility, oligomenorrhea, and amenorrhea. There is also some concern that sustained hyperprolactinemia may predispose to both osteoporosis and breast cancer. When clinically feasible, dose reduction, switching to a prolactin-sparing agent (e.g., aripiprazole), adding a dopamine agonist, or estrogen replacement therapy are possible options to manage this adverse effect.

Cholinergic Effects

Several antipsychotics, particularly low-potency FGAs (e.g., chlorpromazine, thioridazine) and certain SGAs (e.g., cloza-

pine, olanzapine), possess potent muscarinic cholinergic blocking properties. Also, many patients may require antiparkinsonian medications to attenuate neuromotor adverse effects or are also receiving other psychotropic and nonpsychotropic medications with anticholinergic properties. Adverse effects can be peripheral (e.g., blurred vision, dryness of mouth, urinary retention, constipation) or central (e.g., delirium, impaired working memory). Although some patients develop a tolerance to these effects, if symptoms persist, treatment approaches include dose reduction and/or elimination or replacement of other agents with anticholinergic effects. Chewing sugarless gum can alleviate dry mouth, and bethanechol can improve urinary retention.

Hematological Effects

A variety of blood dyscrasias, including leukopenia and agranulocytosis (i.e., granulocyte level $<500/mm^3$), can occur with several antipsychotics. Agranulocytosis is more common with clozapine, which has a box warning for this adverse effect and requires ongoing complete blood count monitoring. When absolute neutrophil counts drop below $1{,}500/mm^3$, the antipsychotic should be stopped, reverse isolation provided, and granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (Gm-CSF) therapy initiated. Rechallenge with clozapine is not recommended.

Sedation

Sedation occurs frequently during early exposure to antipsychotics. Most patients, however, develop tolerance over time. Of note, the olanzapine LAI formulation requires monitoring of patients for 3 hours after administration due to the risk of a postinjection sedation/delirium syndrome. Patients who experience persistent sedation often give this as a reason for discontinuing their antipsychotic. In the early phases of treatment, individuals should be cautioned about driving or operating machinery until they acclimate to the sedating effects. When clinically feasible, reducing the dose or switching to an agent with less propensity to cause this effect is also an option.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a disorder of temperature regulation and neuromotor control that can occur with any antipsychotic. The most common symptoms include muscle rigidity, altered consciousness, and autonomic changes (e.g., fluctuating blood pressure, tachypnea, diaphoresis). Most patients also experience elevated creatine phosphokinase levels. Untreated, the mortality rate is about 20%. Risk factors may include agitation, dehydration, and combined use with other agents (e.g., lithium). Treatment involves early recognition and cessation of the offending agent(s); medical supportive measures such as cooling blankets, ice packs, or ice water enemas; supplemental oxygen; and, when appropriate, agents such as dantrolene, bromocriptine, amantadine, benzodiazepines, or some combination of these. If reintroduction of an antipsychotic is necessary, low doses, gradual titration, and prophylactic bromocriptine are appropriate precautions.

Seizures

Although most antipsychotics lower the seizure threshold in animals, the incidence of seizures in humans is uncommon. When a seizure does occur, it is usually a

single isolated episode. Clozapine carries a box warning for this adverse effect, with the incidence reported to be about 5% at dosages above 600 mg/day. Management strategies include the use of lower doses and/or adding an anticonvulsant agent such as lamotrigine.

Drug Interactions

Clinically relevant drug interactions can occur when antipsychotics are combined with various psychotropic and nonpsychotropic agents. These interactions may be based on pharmacokinetics (e.g., cytochrome P450 [CYP] 2D6 enzyme inhibition with certain SSRIs may slow an antipsychotic drug's metabolism; CYP3A/4 enzyme stimulation with carbamazepine may accelerate an antipsychotic drug's metabolism) or pharmacodynamics (e.g., combining drugs that produce muscarinic cholinergic blockade, thus enhancing anticholinergic adverse effects). Minimizing polypharmacy and making appropriate dose adjustments to compensate for these effects are strategies to reduce negative outcomes.

Conclusion

The modern era of drug treatment for schizophrenia and related psychotic disorders has dramatically improved the lives of our patients. Many would argue, however, that since the introduction of chlorpromazine and, later, clozapine, little progress has been made in terms of enhancing efficacy. Perhaps this is inevitable given the lack of reliable biological markers to facilitate accurate diagnosis, allowing for a more effective identification of various subgroups of psychotic presentations categorized under the umbrella term of schizophrenia. The genetic, neuroimaging, and early identification initiatives now being actively pursued will lead to more specific, more effective, and better tolerated drug therapies. These initiatives will ultimately dictate novel strategies that promise to transform the lives of our patients for the better.

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PART III

Bipolar and Related Disorders and Depressive Disorders

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Since the writing of the fourth edition of this book, there have been a number of advances in both pharmacological and nonpharmacological treatment of mood disorders. Advances include the following:

- The availability of new antidepressants (e.g., vilazodone, transdermal selegiline, levomilnacipran, vortioxetine), new second-generation antipsychotics with mood effects (e.g., asenapine, lurasidone), and new derivatives of existing medications (e.g., desvenlafaxine), and emergence of a broadened evidence base for several nutraceuticals (e.g., L-methylfolate, S-adenosylmethionine, *N*-acetylcysteine).
- Controlled trial data supporting both short- and long-term use of several second-generation antipsychotics in nonpsychotic mood disorders.
- The growth of novel forms of brain stimulation (e.g., repetitive transcranial magnetic stimulation, low-field magnetic stimulation).
- Observations that while some anticonvulsant drugs demonstrate "mood stabilizing" efficacy to treat or prevent manias or depressions (notably, divalproex, carbamazepine, and lamotrigine), most newer anticonvulsants since the development of DSM-IV have been shown *not* to differ from placebo in the treatment of the mood symptoms of bipolar disorder. These medications, however, may distinctively possess other psychotropic properties, such as anxiolysis or antinociception (e.g., gabapentin, pregabalin), or efficacy for binge-eating (e.g., topiramate, zonisamide) or alcohol and other substance use disorders (e.g., topiramate, gabapentin).

- The growth of novel psychotropic targets to treat mood disorders, such as glutamate antagonists (e.g., ketamine, riluzole) and agents such as armodafinil or scopolamine.

A key change in DSM-5 from DSM-IV (and DSM-IV-TR) regarding the diagnosis and treatment of major mood disorders involves a loosening of the boundary between unipolar and bipolar disorders, as illustrated by the "with mixed features" specifier now applicable to both bipolar mania (as well as hypomania) and unipolar major depression, replacing the DSM-IV construct of bipolar I "mixed episodes." This innovation reflects findings from several large-scale studies that have observed subthreshold features of mania or hypomania in up to 40% of individuals whose symptoms meet DSM-IV criteria for unipolar major depression (e.g., Angst et al. 2010).

Other primary changes to the diagnosis of major depressive disorder in DSM-5, as outlined more fully in Boxes 1 and 2, include the following:

- Inclusion of the specifier "with anxious distress" (see Box 1)
- Change of "postpartum onset" specifier to "peripartum onset" specifier (see Box 1)
- Elimination of bereavement as an exclusionary criterion for diagnosing major depression, with clarification that when emotional or physiological responses to a significant loss (e.g., financial ruin, serious medical disabilities) go beyond normal feelings of sadness, rumination, or disrupted sleep (or a possible stress response syndrome [formerly classified as an adjustment disorder with depressed mood in DSM-IV [American Psychiatric Association 1994]), the diagnosis of major depression "should be carefully considered" on the basis of factors such as an individual's past history, a disproportionate level of response to loss, and cultural norms
- Separation of psychotic features from severity ratings, such that major depression with psychotic features is not necessarily severe in all cases

Several other major conceptual changes for diagnosing bipolar disorder have been made in DSM-5 (see Box 3):

- Criterion A now includes "increased goal-directed activity or energy" as a necessary feature for defining a manic or hypomanic episode (reflecting a growing database that psychomotor activation and acceleration are central features that differentiate bipolar from unipolar disorder).
- The addition of the specifier "with anxious distress" (as in major depressive disorder) reflects the growing recognition that prominent anxiety states or disorders are common in both bipolar and unipolar disorders
- A hierarchy has been included that gives precedence to mood-incongruent psychotic features, allowing classification of cases in which mood-congruent and mood-incongruent psychotic features coexist.
- Mania or hypomania arising soon after initiation of an antidepressant, designated as a "substance-induced mood disorder" in DSM-IV, is now recognized as sufficient for making a diagnosis of a manic (or hypomanic) episode, and therefore a bipolar I diagnosis, provided that the manic (or hypomanic) symptoms persist beyond the time frame for resolution of the physiological effects of the medication once it has been stopped.

Box 1. DSM-5 Specifiers for Bipolar and Related Disorders and Depressive Disorders

Specify if:

With anxious distress: The presence of at least two of the following symptoms during the majority of days of the current or most recent episode of mania, hypomania, or depression:

1. Feeling keyed up or tense.
2. Feeling unusually restless.
3. Difficulty concentrating because of worry.
4. Fear that something awful may happen.
5. Feeling that the individual might lose control of himself or herself.

Specify current severity:

Mild: Two symptoms.

Moderate: Three symptoms.

Moderate-severe: Four or five symptoms.

Severe: Four or five symptoms with motor agitation.

Note: Anxious distress has been noted as a prominent feature of both bipolar and major depressive disorder in both primary care and specialty mental health settings. High levels of anxiety have been associated with higher suicide risk, longer duration of illness, and greater likelihood of treatment nonresponse. As a result, it is clinically useful to specify accurately the presence and severity levels of anxious distress for treatment planning and monitoring of response to treatment.

With mixed features: The mixed features specifier can apply to the current manic, hypomanic, or depressive episode in bipolar I or bipolar II disorder:

Manic or hypomanic episode, with mixed features:

A. Full criteria are met for a manic episode or hypomanic episode, and at least three of the following symptoms are present during the majority of days of the current or most recent episode of mania or hypomania:
   1. Prominent dysphoria or depressed mood as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
   2. Diminished interest or pleasure in all, or almost all, activities (as indicated by either subjective account or observation made by others).
   3. Psychomotor retardation nearly every day (observable by others; not merely subjective feelings of being slowed down).
   4. Fatigue or loss of energy.
   5. Feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick).

B. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

C. Mixed symptoms are observable by others and represent a change from the person's usual behavior.

D. For individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features, due to the marked impairment and clinical severity of full mania.

E. The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment).

Depressive episode, with mixed features:

A. Full criteria are met for a major depressive episode, and at least three of the following manic/hypomanic symptoms are present during the majority of days of the current or most recent episode of depression:
   1. Elevated, expansive mood.
   2. Inflated self-esteem or grandiosity.
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Increase in energy or goal-directed activity (either socially, at work or school, or sexually).
   6. Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
   7. Decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted with insomnia).

B. Mixed symptoms are observable by others and represent a change from the person's usual behavior.

C. For individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features.

D. The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment).

Note: Mixed features associated with a major depressive episode have been found to be a significant risk factor for the development of bipolar I or bipolar II disorder. As a result, it is clinically useful to note the presence of this specifier for treatment planning and monitoring of response to treatment.

With rapid cycling (can be applied to bipolar I or bipolar II disorder): Presence of at least four mood episodes in the previous 12 months that meet the criteria for manic, hypomanic, or major depressive episode.

Note: Episodes are demarcated by either partial or full remissions of at least 2 months or a switch to an episode of the opposite polarity (e.g., major depressive episode to manic episode).

Note: The essential feature of a rapid-cycling bipolar disorder is the occurrence of at least four mood episodes during the previous 12 months. These episodes can occur in any combination and order. The episodes must meet both the duration and symptom number criteria for a major depressive, manic, or hypomanic episode and must be demarcated by either a period of full remission or a switch to an episode of the opposite polarity. Manic and hypomanic episodes are counted as being on the same pole. Except for the fact that they occur more frequently, the episodes that occur in a rapid-cycling pattern are no different from those that occur in a non-rapid-cycling pattern. Mood episodes that count toward defining a rapid-cycling pattern exclude those episodes directly caused by a substance (e.g., cocaine, corticosteroids) or another medical condition.

With melancholic features:

A. One of the following is present during the most severe period of the current episode:
   1. Loss of pleasure in all, or almost all, activities.
   2. Lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens).

B. Three (or more) of the following:

1. A distinct quality of depressed mood characterized by profound despondency, despair, and/or moroseness or by so-called empty mood.
2. Depression that is regularly worse in the morning.
3. Early-morning awakening (i.e., at least 2 hours before usual awakening).
4. Marked psychomotor agitation or retardation.
5. Significant anorexia or weight loss.
6. Excessive or inappropriate guilt.

Note: The specifier "with melancholic features" is applied if these features are present at the most severe stage of the episode. There is a near-complete absence of the capacity for pleasure, not merely a diminution. A guideline for evaluating the lack of reactivity of mood is that even highly desired events are not associated with marked brightening of mood. Either mood does not brighten at all, or it brightens only partially (e.g., up to 20%–40% of normal for only minutes at a time). The "distinct quality" of mood that is characteristic of the "with melancholic features" specifier is experienced as qualitatively different from that during a nonmelancholic depressive episode. A depressed mood that is described as merely more severe, longer lasting, or present without a reason is not considered distinct in quality. Psychomotor changes are nearly always present and are observable by others.

Melancholic features exhibit only a modest tendency to repeat across episodes in the same individual. They are more frequent in inpatients, as opposed to outpatients; are less likely to occur in milder than in more severe major depressive episodes; and are more likely to occur in those with psychotic features.

With atypical features: This specifier can be applied when these features predominate during the majority of days of the current or most recent major depressive episode.

A. Mood reactivity (i.e., mood brightens in response to actual or potential positive events).

B. Two (or more) of the following features:

1. Significant weight gain or increase in appetite.
2. Hypersomnia.
3. Leaden paralysis (i.e., heavy, leaden feelings in arms or legs).
4. A long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment.

C. Criteria are not met for "with melancholic features" or "with catatonia" during the same episode.

Note: "Atypical depression" has historical significance (i.e., atypical in contradistinction to the more classical agitated, "endogenous" presentations of depression that were the norm when depression was rarely diagnosed in outpatients and almost never in adolescents or younger adults) and today does not connote an uncommon or unusual clinical presentation as the term might imply.

Mood reactivity is the capacity to be cheered up when presented with positive events (e.g., a visit from children, compliments from others). Mood may become euthymic (not sad) even for extended periods of time if the external circumstances remain favorable. Increased appetite may be manifested by an obvious increase in food intake or by weight gain. Hypersomnia may include either an extended period of nighttime sleep or daytime napping that totals at least 10 hours of sleep per day (or at least 2 hours more than when not depressed). Leaden paralysis is defined as feeling heavy, leaden, or weighted down, usually in the arms or legs. This sensation is generally present for at least an hour a day but often lasts for many hours at a

time. Unlike the other atypical features, pathological sensitivity to perceived interpersonal rejection is a trait that has an early onset and persists throughout most of adult life. Rejection sensitivity occurs both when the person is and is not depressed, though it may be exacerbated during depressive periods.

With psychotic features: Delusions or hallucinations are present at any time in the episode. If psychotic features are present, specify if mood-congruent or mood-incongruent:

With mood-congruent psychotic features: During manic episodes, the content of all delusions and hallucinations is consistent with the typical manic themes of grandiosity, invulnerability, etc., but may also include themes of suspiciousness or paranoia, especially with respect to others' doubts about the individual's capacities, accomplishments, and so forth.

With mood-incongruent psychotic features: The content of delusions and hallucinations is inconsistent with the episode polarity themes as described above, or the content is a mixture of mood-incongruent and mood-congruent themes.

With catatonia: This specifier can apply to an episode of mania or depression if catatonic features are present during most of the episode. See criteria for catatonia associated with a mental disorder in the chapter "Schizophrenia Spectrum and Other Psychotic Disorders."

With peripartum onset: This specifier can be applied to the current or, if the full criteria are not currently met for a mood episode, most recent episode of mania, hypomania, or major depression in bipolar I or bipolar II disorder if onset of mood symptoms occurs during pregnancy or in the 4 weeks following delivery.

Note: Mood episodes can have their onset either during pregnancy or postpartum. Although the estimates differ according to the period of follow-up after delivery, between 3% and 6% of women will experience the onset of a major depressive episode during pregnancy or in the weeks or months following delivery. Fifty percent of "postpartum" major depressive episodes actually begin prior to delivery. Thus, these episodes are referred to collectively as *peripartum* episodes. Women with peripartum major depressive episodes often have severe anxiety and even panic attacks. Prospective studies have demonstrated that mood and anxiety symptoms during pregnancy, as well as the "baby blues," increase the risk for a postpartum major depressive episode.

Peripartum-onset mood episodes can present either with or without psychotic features. Infanticide is most often associated with postpartum psychotic episodes that are characterized by command hallucinations to kill the infant or delusions that the infant is possessed, but psychotic symptoms can also occur in severe postpartum mood episodes without such specific delusions or hallucinations.

Postpartum mood (major depressive or manic) episodes with psychotic features appear to occur in from 1 in 500 to 1 in 1,000 deliveries and may be more common in primiparous women. The risk of postpartum episodes with psychotic features is particularly increased for women with prior postpartum mood episodes but is also elevated for those with a prior history of a depressive or bipolar disorder (especially bipolar I disorder) and those with a family history of bipolar disorders.

Once a woman has had a postpartum episode with psychotic features, the risk of recurrence with each subsequent delivery is between 30% and 50%. Postpartum episodes must be differentiated from delirium occurring in the postpartum period, which is distinguished by a fluctuating level of awareness or attention. The postpartum period is unique with respect to the degree of neuroendocrine alterations and psychosocial adjustments, the potential impact of breast-feeding on treatment planning, and the long-term implications of a history of postpartum mood disorder on subsequent family planning.

With seasonal pattern: This specifier applies to the lifetime pattern of mood episodes. The essential feature is a regular seasonal pattern of at least one type of episode (i.e., mania, hypomania, or depression). The other types of episodes may not follow this pattern. For example, an individual may have seasonal manias, but his or her depressions do not regularly occur at a specific time of year.

A. There has been a regular temporal relationship between the onset of manic, hypomanic, or major depressive episodes and a particular time of the year (e.g., in the fall or winter) in bipolar I or bipolar II disorder.

Note: Do not include cases in which there is an obvious effect of seasonally related psychosocial stressors (e.g., regularly being unemployed every winter).

B. Full remissions (or a change from major depression to mania or hypomania or vice versa) also occur at a characteristic time of the year (e.g., depression disappears in the spring).
C. In the last 2 years, the individual's manic, hypomanic, or major depressive episodes have demonstrated a temporal seasonal relationship, as defined above, and no non-seasonal episodes of that polarity have occurred during that 2-year period.
D. Seasonal manias, hypomanias, or depressions (as described above) substantially outnumber any nonseasonal manias, hypomanias, or depressions that may have occurred over the individual's lifetime.

Note: This specifier can be applied to the pattern of major depressive episodes in bipolar I disorder, bipolar II disorder, or major depressive disorder, recurrent. The essential feature is the onset and remission of major depressive episodes at characteristic times of the year. In most cases, the episodes begin in fall or winter and remit in spring. Less commonly, there may be recurrent summer depressive episodes. This pattern of onset and remission of episodes must have occurred during at least a 2-year period, without any nonseasonal episodes occurring during this period. In addition, the seasonal depressive episodes must substantially outnumber any nonseasonal depressive episodes over the individual's lifetime.

This specifier does not apply to those situations in which the pattern is better explained by seasonally linked psychosocial stressors (e.g., seasonal unemployment or school schedule). Major depressive episodes that occur in a seasonal pattern are often characterized by loss of energy, hypersomnia, overeating, weight gain, and a craving for carbohydrates. It is unclear whether a seasonal pattern is more likely in recurrent major depressive disorder or in bipolar disorders. However, within the bipolar disorders group, a seasonal pattern appears to be more likely in bipolar II disorder than in bipolar I disorder. In some individuals, the onset of manic or hypomanic episodes may also be linked to a particular season.

The prevalence of winter-type seasonal pattern appears to vary with latitude, age, and sex. Prevalence increases with higher latitudes. Age is also a strong predictor of seasonality, with younger persons at higher risk for winter depressive episodes.

Specify if:

In partial remission: Symptoms of the immediately previous manic, hypomanic, or depressive episode are present, but full criteria are not met, or there is a period lasting less than 2 months without any significant symptoms of a manic, hypomanic, or major depressive episode following the end of such an episode.

In full remission: During the past 2 months, no significant signs or symptoms of the disturbance were present.

Specify current severity:

Severity is based on the number of criterion symptoms, the severity of those symptoms, and the degree of functional disability.

Mild: Few, if any, symptoms in excess of those required to meet the diagnostic criteria are present, the intensity of the symptoms is distressing but manageable, and the symptoms result in minor impairment in social or occupational functioning.

Moderate: The number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for "mild" and "severe."

Severe: The number of symptoms is substantially in excess of those required to make the diagnosis, the intensity of the symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning.

Box 2. DSM-5 Diagnostic Criteria for Major Depressive Episode

Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

   Note: Do not include symptoms that are clearly attributable to another medical condition.

   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
   3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
   4. Insomnia or hypersomnia nearly every day.
   5. Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down).
   6. Fatigue or loss of energy nearly every day.
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or another medical condition.

Note: Criteria A–C constitute a major depressive episode. Major depressive episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive

episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.[1]

Box 3. DSM-5 Diagnostic Criteria for Manic Episode and Hypomanic Episode

Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
   7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

[1]In distinguishing grief from a major depressive episode (MDE), it is useful to consider that in grief the predominant affect is feelings of emptiness and loss, while in MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves, the so-called pangs of grief. These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of a MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of a major depressive episode. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than the self-critical or pessimistic ruminations seen in a MDE. In grief, self-esteem is generally preserved, whereas in a MDE, feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis-à-vis the deceased (e.g., not visiting frequently enough, not telling the deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such thoughts are generally focused on the deceased and possibly about "joining" the deceased, whereas in a major depressive episode such thoughts are focused on ending one's own life because of feeling worthless, undeserving of life, or unable to cope with the pain of depression.

Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.
Note: Criteria A–D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

Hypomanic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.
B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
   7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.
D. The disturbance in mood and the change in functioning are observable by others.
E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.
F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment).
   Note: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

Note: Criteria A–F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

Other DSM-5 specifiers for mood disorders are summarized in Box 1. The construct of cyclothymic disorder remains unchanged from DSM-IV to DSM-5.

Several other significant changes to the mood disorders section from DSM-IV to DSM-5 have been made:

- A new diagnostic entity, *disruptive mood dysregulation disorder,* was added (see Box 4). This diagnosis can be considered for individuals ages 6–18 years who present with severe recurrent temper outbursts with intermittent irritable or angry mood, but whose

symptoms never meet lifetime criteria for a manic or hypomanic episode, oppositional defiant disorder, or intermittent explosive disorder.

- *Premenstrual dysphoric disorder* has been moved from the appendix of DSM-IV-TR (as a proposed condition "provided for further study") to Section II of DSM-5, with articulation of formal criteria, for which expert treatment guidelines advocate the first-line use of selective serotonin reuptake inhibitors (SSRIs) "continuously throughout the entire month, intermittently from ovulation to the onset of menstruation, or semi-intermittently with dosage increases during the late luteal phase" (Steiner et al. 2006).

Box 4. DSM-5 Diagnostic Criteria for Disruptive Mood Dysregulation Disorder

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A. Severe recurrent temper outbursts manifested verbally (e.g., verbal rages) and/or behaviorally (e.g., physical aggression toward people or property) that are grossly out of proportion in intensity or duration to the situation or provocation.
B. The temper outbursts are inconsistent with developmental level.
C. The temper outbursts occur, on average, three or more times per week.
D. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observable by others (e.g., parents, teachers, peers).
E. Criteria A–D have been present for 12 or more months. Throughout that time, the individual has not had a period lasting 3 or more consecutive months without all of the symptoms in Criteria A–D.
F. Criteria A and D are present in at least two of three settings (i.e., at home, at school, with peers) and are severe in at least one of these.
G. The diagnosis should not be made for the first time before age 6 years or after age 18 years.
H. By history or observation, the age at onset of Criteria A–E is before 10 years.
I. There has never been a distinct period lasting more than 1 day during which the full symptom criteria, except duration, for a manic or hypomanic episode have been met.
   Note: Developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation, should not be considered as a symptom of mania or hypomania.
J. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by another mental disorder (e.g., autism spectrum disorder, posttraumatic stress disorder, separation anxiety disorder, persistent depressive disorder [dysthymia]).
   Note: This diagnosis cannot coexist with oppositional defiant disorder, intermittent explosive disorder, or bipolar disorder, though it can coexist with others, including major depressive disorder, attention-deficit/hyperactivity disorder, conduct disorder, and substance use disorders. Individuals whose symptoms meet criteria for both disruptive mood dysregulation disorder and oppositional defiant disorder should only be given the diagnosis of disruptive mood dysregulation disorder. If an individual has ever experienced a manic or hypomanic episode, the diagnosis of disruptive mood dysregulation disorder should not be assigned.
K. The symptoms are not attributable to the physiological effects of a substance or to another medical or neurological condition.

The treatment of DSM-5 mood disorders is informed partly by two large, multi-site National Institute of Mental Health–funded programs that occurred after publication of DSM-IV-TR: the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). As discussed further in the chapters in Part III, these landmark trials revealed a much greater frequency of relapse and treatment resistance than many clinicians might previously have imagined across both bipolar and unipolar disorders. The findings of these studies have perhaps taught us less about what specifically to *do* than about what not to take for granted when treating complex mood disorders. For example, the STEP-BD showed that for most individuals with bipolar depression, adding an antidepressant to an antimanic drug is likely to be neither helpful nor harmful, pointing to a compelling need for the development of novel therapeutic strategies for bipolar depression. STAR*D challenged conventional wisdom that broadening the breadth of spectrum in monoaminergic neurotransmitter targets in major depression (e.g., serotonin-norepinephrine reuptake inhibitors [SNRIs], monoamine oxidase inhibitors [MAOIs]) routinely improves outcomes when first-line SSRIs yield inadequate results. Decisions about successive treatment approaches for complex mood disorders have themselves become more complex and likely depend on individualized strategies tailored to unique characteristics of a given patient. (For example, such decisions must take into account comorbid conditions such as anxiety or substance use disorders, subthreshold signs of bipolar disorder or psychosis, and the ever-challenging balance between efficacy and tolerability, particularly with respect to concerns about adverse sexual effects, metabolic dysfunction and weight gain.)

Many core treatments for major depressive episodes and manic or hypomanic episodes will entail little change when DSM-5, rather than DSM-IV, diagnostic criteria are being applied, with several notable exceptions, as discussed in the following chapters. Perhaps one area of greatest advance has been in the development of evidence-based focused psychotherapies for depression, as described by Michael Thase and colleagues in Chapter 12 ("Psychotherapy of Mood Disorders"). These focused psychotherapies are often used in concert with pharmacotherapies, as a potent strategy to hasten recovery and demonstrably improve functional outcomes. Clinical trials in mood disorder research have increasingly pointed to the need for studies not just to target mood symptoms but also to integrate work and social functioning as part of defined primary outcomes.

Areas that have represented the greatest unmet needs in the treatment of mood disorders since DSM-IV emerged have largely persisted and acquired greater complexity. For instance, effective remedies remain elusive for rapid-cycling bipolar disorder—a phenomenon that was once thought mainly to reflect poor response to lithium maintenance therapy but that now has become more indicative of poor response in general to mood stabilizer monotherapies or even combination therapies, as described by Terence Ketter and colleagues in Chapter 13 ("Acute and Maintenance Treatment of Bipolar and Related Disorders"). Antidepressant use remains controversial in bipolar depression, but debate has shifted somewhat in recent years mainly from concerns about the potential of antidepressants to induce mania or cycle acceleration as a common occurrence to, more frequently, the sheer lack of efficacy of

these medications in bipolar depression, or to delineating the profile of patients for whom antidepressants may worsen outcomes (e.g., in the setting of mixed features or rapid cycling).

As described in Chapter 14 ("Pharmacological and Somatic Treatments for Major Depressive Disorder") by Mark Niciu and colleagues, new, emerging directions are poised to move therapeutics beyond nominal alterations of existing drugs that merely target monoaminergic systems (e.g., SSRIs, MAOIs, SNRIs and tricyclic antidepressants), to a growing focus on other agents, including antiglutamatergic agents, glycine transporter inhibitors, cholinergic antagonists, immunomodulators, and novel neuropeptide antagonists.

Finally, in Chapter 15 ("Brain Stimulation Treatments for Mood Disorders"), Mark George and colleagues discuss advances in novel forms of brain stimulation, an area that has struggled to refine technologies that rival electroconvulsive therapy with respect to efficacy but that may yield greater feasibility, tolerability, and incorporation as a more mainstream component in the everyday armamentarium against complex mood disorders.

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CHAPTER 12

Psychotherapy of Mood Disorders

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Psychotherapy has a long history in the treatment of mood disorders. Only in the past 20 years have manualized psychotherapies been submitted to empirical evaluation in randomized trials. In this chapter, we highlight several methods that have been found to be effective in unipolar and bipolar disorders: cognitive therapy, interpersonal and social rhythm therapy, psychodynamic psychotherapy, family-based interventions (including family focused therapy), and group psychotherapy. Although the coverage is not exhaustive, the reader will see common threads in the way that mood disorders are approached in psychotherapy.

Cognitive Therapy

First developed by psychiatrist Aaron T. Beck more than 40 years ago, cognitive therapy (CT) is one of the most influential and by far the best studied systems of psychotherapy for people with depres-

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sive disorders. CT is usually thought of as a time-limited therapy, and most studies of depression have evaluated the efficacy of CT over a 3- to 4-month period. A member of a larger group of related cognitive-behavioral therapies (CBT), Beck's CT is distinguished by the cognitive model of psychopathology—specifically, that distortions in information processing and maladaptive ways of thinking about oneself, the world, and the future (i.e., the cognitive triad) foster and maintain a wide range of disorders of mood and behavior. Although initially developed for treatment of depression (Beck et al. 1979), CT has been modified for treatment of bipolar disorder, various anxiety disorders, personality disorders, substance abuse disorders, and schizophrenia.

Across disorders, CT is characterized by 1) use of explicit methods to educate patients about the cognitive model as it pertains to their illness and how to apply specific methods to improve one's ability to cope; 2) a pragmatic therapeutic style that is active and collaborative; 3) use of structure to help organize and pace sessions; and 4) use of homework to extend the process of therapy outside of the therapist's office.

For treatment of depression, specific behavioral methods include behavioral activation strategies, such as graded task assignments and the use of activity scheduling, which are aimed at increasing involvement in activities that promote feelings of mastery and pleasure. Although use of behavioral strategies may predominate early in the course of treatment, cognitive methods sometimes are initiated during the first session and include exercises tailored to help the depressed person recognize the relationship between negative moods and "silent" cognitive distortions and to begin to test out alternative ways to think about problems or other troubling circumstances. The Daily Record of Dysfunctional Thoughts (DRDT), which provides columns to record activities, mood, automatic negative thoughts, more rational (i.e., less distorted) responses, and the impact of the exercise on the negative mood, is one iconic method for teaching this approach to cognitive restructuring. In this chapter, the theory and basic techniques of CT for treatment of depression will be reviewed, and the treatment outcome research literature will be briefly summarized.

The Cognitive Model of Depression

The cognitive model of depression posits that characteristic errors in information processing trigger and sustain states of emotional distress (Beck 1976). Indeed, Beck playfully tweaked one of Freud's adages about making the unconscious conscious when he suggested that *affect was the "royal road" to cognition*. Thus, therapists initially teach depressed patients to use periods of sad or low mood to look for examples of negative thinking (i.e., "hot" thoughts). Such automatic negative thoughts, which occur instantaneously and are tacitly assumed to represent the "truth," can take the form of words or images, which in turn can be collated and organized by themes to suggest "deeper" cognitive structures such as attitudes, beliefs, and schemas. *Schemas*, drawn from the work of Piaget, represent the most basic or fundamental organizing principles that silently guide decision-making and one's sense of well-being. These often silent vulnerabilities also may be uncovered by the occurrence of relevant life events. The most common dysfunctional attitudes also can be identified by having the patient fill out the Dysfunctional Attitude Scale. For most people

seeking treatment for depression, schemas pertaining to one's lovability ("No one will ever truly love me") and one's vocational, occupational, or intellectual abilities ("No matter how hard I try, I always fail") are most salient.

Dysfunctional cognitive processes also contribute to psychopathology by biasing information processing or access to memories. For example, a depressed mood is associated with a selective recall of negative (i.e., mood-congruent) memories, and a disproportionate tendency to overlook, minimize, or disqualify alternative, more positive explanations for an upsetting event. In terms of attributions (i.e., meanings ascribed to events), people prone to depression are more likely to see negative events as personal, relatively irreversible, and having long-standing consequences.

For individuals with bipolar disorder, switches into hypomania or mania are characteristically accompanied by mood-congruent cognitive changes that can include underestimation of risks, overestimating opportunities and/or probabilities for success, and a reduced ability to perceive the impact that one's behavior has on others (Basco and Rush 2005). For individuals with bipolar disorder, for whom loss of insight and irritability and grandiosity associated with worsening mania can complicate therapy, identification of early warning signs and self-monitoring are often more useful therapeutic strategies than those aimed at restructuring distorted cognitions.

Therapeutic Strategies

A course of CT for mood disorders typically consists of 12–20 individual sessions conducted over 3–4 months. Although most practitioners see patients weekly, twice-weekly sessions are recommended for treatment of more severe depressions. As termination of a successful course of therapy nears, many therapists will space out the final few sessions to ensure that the patient is able to maintain the benefits of therapy without regular therapeutic contact.

Group models of CT also have been introduced and tested against individual therapy in clinical trials. One could argue that, given the limited number of CT therapists in some communities, group CT represents the best way to make the benefits of this form of treatment more readily available. As noted further in the "Group Psychotherapy" section of this chapter, the structured and educational nature of CT is well suited to group delivery, although it can be a challenge for "open" groups with patients with varying levels of practice and sophistication with CT techniques.

The therapist maintains a relatively high activity level and is responsible to guide or pace the flow of the sessions. All CT sessions begin with setting an agenda and a review of the patient's symptomatic status. All CT sessions end with the therapist eliciting feedback about the session ("How do you feel about today's session?") and making a homework or self-help assignment. These assignments are logical extensions of the material discussed in sessions and should clearly demonstrate that this therapy involves more work outside of the consultation room than inside. As homework nonadherence is a strong predictor of poorer outcomes, reviewing homework assignments and trouble-shooting problems as they emerge is a critical aspect of therapy.

In addition to high therapist activity, which is common to most types of CBT, therapists trained in Beck's model of therapy make ample use of Socratic questioning to encourage the patient to take an active role in the process of applying the cognitive model to their own thoughts

and feelings. The process of working together to identify functional relationships between thinking or certain maladaptive behavior and changes in feeling states, selectively building on strategies that work and moving on when a strategy isn't much help, is sometimes referred to "personal science" or "collaborative empiricism."

Because CT does not view the therapeutic relationship as the *primary* vehicle for therapeutic change, it is sometimes misperceived to minimize the therapeutic relationship. Indeed, novice therapists may place too much value on techniques and not enough on maintaining a strong therapeutic alliance. That said, an experienced and skilled therapist will be mindful of signs of strains or ruptures in the therapeutic alliance and address them in a manner that is consistent with the overall model of therapy ("I noticed that you don't seem too happy with me right now. Do you mind if we talk a little about what's happening right now, between you and me?").

Therapists vary widely with respect to how often behavioral strategies are used in CT. Most therapists make greater use of behavioral strategies during the first few weeks of therapy and the process of activity scheduling and behavioral charting, which typically begins during the first week of therapy, and serves as a useful way to help depressed people begin to identify associations between automatic negative thoughts and depressed mood. Typically introduced at the end of the first session of therapy, the pamphlet *Coping With Depression* (Beck et al. 1995) includes an activity schedule that enables patients to begin to track what they are doing in relation to how they are feeling and what they are thinking about. By the second or third session, the patient is asked to begin to plan to do more activities that are chosen to increase feelings of mastery (M) and pleasure (P). The intended result of these simple behavioral assignments is that most people will feel less depressed and will gain some lift in morale associated with being able to do more. Graded task assignments are an extension of these planned activities and are used to help patients begin to tackle more demanding and complex tasks or problems. The simple rationale for this strategy is that even in a depressed state, it is easier to complete overwhelming tasks when they are broken down into smaller steps or components.

A third simple strategy, the Coping Card, can help facilitate shifting therapeutic focus from behaviors to cognitions. Whether written on a 3×5 index card or a message application of a smart phone, a Coping Card provides a brief, scripted rational response that the patient can use when experiencing automatic negative thoughts.

Most CT therapists will try to shape the pace of therapy so that strategies to recognize and modify automatic thoughts are introduced by the third or fourth session of therapy. This process is facilitated in sessions when the therapist observes a shift in mood or behavior that is likely to be accompanied by an automatic negative thought. As noted earlier, Socratic questioning and thought recording, as exemplified by the DRDT worksheet, are two of the most widely used methods to identify and test the veracity of automatic negative thoughts (Wright et al. 2006).

Some depressed people truly enjoy learning to label the particular type of cognitive distortion reflected by the automatic negative thought, whereas others do not. At the end of the day, it is not essential to correctly identify overgeneralization versus black-or-white thinking.

Instead, it is essential to be able to recognize shifts in mood, identify negative thoughts, and gain skill in testing the accuracy of those thoughts and considering more rational alternatives.

Learning CT in the Second Decade of the 21st Century

Although most mental health practitioners trained during the past 20 years have some working knowledge of CT, there is reason to believe that relatively few are actually expert in this model of therapy. This is true even for those who have some supervised experience during training: without advanced supervision and some sense of professional identity as a cognitive therapist, the path of least resistance for most therapists is to revert to more conventional, less directional therapies.

One invaluable source for advanced training is the extramural fellowship program of The Beck Institute (Web site: www.beckinstitute.org). The Web site of The Academy of Cognitive Therapy (www.academyofct.org) is also a useful resource. Other training programs are listed in the book *Learning Cognitive-Behavior Therapy: An Illustrated Guide* (Wright et al. 2006).

Outcome Studies

The efficacy of CT has been subjected to dozens of controlled investigations across a wide range of depressive disorders (see, e.g., Butler et al. 2006). Meta-analyses of early studies tended to support the notion that not only was CT an efficacious treatment of depression (i.e., consistently superior to wait-list or nonspecific contact control conditions), but also it was more effective after 3–4 months of treatment than antidepressant pharmacotherapy or nondirective psychotherapy (Dobson 1989; Robinson et al. 1990). In retrospect, the early studies were affected to some extent by allegiance bias and the so-called Lourdes effect (Gaffan et al. 1995), and subsequent studies, which made greater efforts to ensure that all treatments were adequately administered, found CT to be comparably effective to antidepressant pharmacotherapy (DeRubeis et al. 2005; Dimidjian et al. 2006; Elkin et al. 1989; Hollon et al. 1992; Jarrett et al. 1999; Thase et al. 2007), interpersonal psychotherapy (Elkin et al. 1989), and behavior therapy (Dimidjian et al. 2006).

Although CT is unlikely to be more effective than competently administered pharmacotherapy in the short run, there is evidence from follow-up studies that the effects of successful treatment with CT are significantly more durable or long-lasting—after treatment is stopped—than those of pharmacotherapy (see, e.g., Vittengl et al. 2007). Across 1 year, patients who respond to time-limited CT have about the same relapse rate as do patients who responded to antidepressants and who are receiving continuation-phase pharmacotherapy (Hollon et al. 2005). As such, the cost-effectiveness profile of CT grows more favorable over time.

Three studies tested the sequential use of CT following successful treatment with antidepressant pharmacotherapy (Fava et al. 1996, 1998; Paykel et al. 1999). In each case, patients receiving adjunctive CT were significantly less likely to have a relapse or recurrence of their symptoms than patients who received only antidepressant medication. Furthermore, in the small study of recurrent depression by Fava et al. (1998), treatment with CT significantly increased the chances of successfully discontinuing antidepressant medication.

With respect to adjunctive treatment of bipolar depressive episodes, one small study conducted in Australia (Ball et al. 2006) and a larger multicenter study conducted in the United States as part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD; Miklowitz et al. 2007a; Miklowitz et al. 2007b) found that the addition of CT to ongoing therapy with mood stabilizers significantly improved depressive symptoms. Given the uncertainty surrounding the use of antidepressants to treat bipolar depressive episodes, these promising findings warrant further attention. Two larger scale studies of the value of CT for relapse prevention in bipolar I disorder produced conflicting results, with Lam et al. (2003) observing a very strong effect favoring adjunctive CT during the first year of follow-up, but Scott et al. (2006) finding no consistent benefit for adjunctive CT. Interestingly, on a secondary analysis, Scott et al. (2006) found that the effects of adjunctive CT interacted with disease chronicity such that patients who had had relatively few episodes experienced some prophylactic effects, whereas those with a history of numerous prior bipolar episodes actually did somewhat worse than the control group over time.

Summary

Beck's model of CT is the best-studied and most influential of the first generation of time-limited, depression-focused therapies. Although the initial promise that CT may prove to be a more effective acute-phase therapy for patients with mild-to-moderate episodes of major depressive disorder than other existing standard therapies has not been confirmed by a newer generation of research, CT is at least as effective as other standard therapies and appears to have more durable or long-lasting benefits—after treatment is stopped—than do antidepressant medications.

Interpersonal and Social Rhythm Therapy

Interpersonal and social rhythm therapy (IPSRT) is an empirically supported treatment for bipolar disorders developed by Ellen Frank and colleagues at the University of Pittsburgh (Frank 2005). IPSRT is considered an adaptation of interpersonal psychotherapy (IPT) for major depressive disorder (Klerman et al. 1984). It fuses with IPT a set of behavioral strategies designed to regulate circadian factors that have been implicated in bipolar mood instability (Ehlers et al. 1988). Based on evidence that interpersonal distress is associated with the maintenance of current mood symptoms and onset of new mood episodes, IPSRT helps patients learn new strategies to resolve current interpersonal and social role problems. IPSRT also focuses on helping patients to develop more regular social rhythms or daily routines as a means of entraining their intrinsic circadian rhythms to external social cues. Both the interpersonal and social rhythm foci of the treatment are intended to reduce current mood symptomatology and to prevent the return of mood symptoms. Data from two large randomized controlled trials, to be discussed later in this section, demonstrate IPSRT's efficacy when used as an individual psychotherapy in combination with medication as a strategy to hasten recovery from depressive episodes and prevent recurrence of new depressive or manic episodes. Uncontrolled data point to its potential utility as a monotherapy for some persons with bipolar II disorder and naturalistic data suggest a role for IPSRT offered in a

group setting for patients with bipolar I and II disorders.

In its original form, the three major goals of IPSRT are to minimize the impact of disruptive life events on social rhythms, address interpersonal difficulties as they arise in the context of a mood disorder, and support medication adherence by means of psychoeducational, interpersonal, and behavioral strategies.

Theoretical Background

The framework of IPSRT rests on three related theoretical constructs: 1) the "instability model" of bipolar disorder proposed by Goodwin and Jamison (1990), 2) theories regarding the function of social and environmental cues in promoting/disrupting circadian rhythm integrity (Ehlers et al. 1988, 1993), and 3) the principles of IPT first conceptualized by Klerman and colleagues (1984).

In their instability model, Goodwin and Jamison (1990) define three interconnected pathways to episode recurrence: taxing life events, medication noncompliance, and social rhythm disruption. Related to the instability model, circadian rhythm researchers have identified reciprocal relationships among circadian rhythms, sleep-wake cycles, and mood. It is well documented—for instance, that sleep reduction can lead to mania in individuals with bipolar disorder (Leibenluft et al. 1996; Wehr et al. 1987).

Attempting to bridge the biological and psychosocial models of depression, we hypothesized that there are specific social cues that entrain biological cycles (*zeitgebers)* and others that disrupt them (*zeitstörers)* (Ehlers et al. 1988). Social zeitgebers are defined as personal relationships, social demands, or tasks that entrain biological rhythms (e.g., a husband who wakes up his wife at 6 A.M. each day as he readies himself for work). We further hypothesized that losing a social zeitgeber (e.g., husband's extended absence from home for work travel with attendant loss of morning wake time) could trigger an episode by causing the dysregulation of biological rhythms (Ehlers et al. 1993). In individuals with a genetic predisposition to mood disorders, the physiological and chronobiological disturbances produced by losing the social cues for sleep and meal times could be as important in the genesis of an episode as the psychological distress generated by the event. In contrast to zeitgebers, zeitstörers are defined as physical, chemical, or psychosocial events that *disturb* the biological clock. For instance, travel across time zones is a prototypical zeitstörer. The abrupt change in the timing of light exposure, rest times, and sleep schedule can produce a range of symptoms from mild "jet lag" to a full-blown affective episode in predisposed individuals. IPSRT was built on the idea that helping patients to regulate social rhythms (i.e., modulate zeitgebers and zeitstörers) may help vulnerable individuals reduce the risk of developing mood symptoms. In IPSRT, therapists use IPT strategies both to resolve interpersonal difficulties and to lessen the impact of stressful interpersonal events on daily routines.

Intervention Strategies

IPSRT fuses three distinct intervention strategies—psychoeducation, social rhythm therapy, and IPT—into a single psychosocial treatment. IPSRT helps patients optimize daily schedules, resolve interpersonal difficulties, and understand their illness in order to achieve symptom remission and improve interpersonal functioning. In practice, however, these strategies are administered flexibly and

fluidly, without distinct boundaries between modalities. Table 12–1 summarizes these three strategies and the treatment techniques associated with them.

TABLE 12–1. IPSRT treatment strategies

Strategy	Techniques
Psychoeducation	Provide education regarding: • Medications and their side effects • Course and symptoms of bipolar disorder Teach patients to recognize: • Early warning signs of recurrence • Prodromal symptoms Encourage patient to: • Become "expert" on their illness • Collaboratively manage illness with therapist and psychiatrist
Social rhythm therapy	Balance stimulation and stability Complete Social Rhythm Metric: • Monitor frequency/intensity of social interactions • Monitor daily mood Search for specific triggers of rhythm disruption Gradually regularize social rhythms
Interpersonal psychotherapy	Conduct in-depth psychiatric evaluation Link mood to life events Establish interpersonal case formulation (focus on one or two problem areas): • Grief • Role transition • Role dispute • Interpersonal deficits Grieve the lost "healthy self"

Psychoeducation

Virtually all bipolar-specific psychotherapies incorporate psychoeducation—albeit to varying degrees and with different points of emphasis. In IPSRT, psychoeducation focuses on a) the illness and its consequences, b) medications and their side effects, and c) prodromal symptoms and detection of early warning symptoms. In the course of IPSRT, patients are encouraged to become "experts" in bipolar disorder so that they can collaborate more effectively in the management of their illness. Therapists are encouraged to work collaboratively with the patient to understand and remedy sources of nonadherence—including management of side effects—that interfere with optimal quality of life.

In order to encourage early identification of prodromal symptoms, the thera-

pist reviews prior episodes of depression and mania with the patient. Jointly, the therapist and patient identify characteristic behaviors or symptoms that may herald the onset of an episode, and agree to routinely assess the patient for these harbingers of exacerbation.

Social Rhythm Therapy

Social rhythm therapy is based on the theory that stable daily rhythms lead to enhanced stability of mood. This component of IPSRT focuses on developing strategies to promote regular, rhythm-entraining, social zeitgebers and to manage the negative impact of disrupting zeistörers. Each week patients are asked to complete the Social Rhythm Metric (SRM), a self-monitoring instrument that helps them optimize their daily rhythms. This 5-item self-report form prompts patients to record five daily activities (i.e., out of bed, first contact with another person, start work/school/volunteer/family care, dinner, to bed) (Ashman et al. 1999), whether each occurred alone or with others present, and whether or not they involved significant amounts of social stimulation (i.e., quiet versus interactive). Patients are also asked to rate their moods each day.

In the beginning stages of treatment, the patient is asked to complete the SRM weekly. The first 3–4 weeks of SRMs are used to establish the patient's baseline social rhythms. The therapist and patient jointly review the SRMs, identifying both stable and unstable daily rhythms. By examining the SRMs, the therapist and patient can begin to identify behaviors that negatively influence the patient's rhythm stability.

Once baseline SRMs are collected and patterns of regularity/irregularity identified, the therapist and patient begin working toward rhythm stability through graded, sequential lifestyle changes. The therapist and patient identify short-term, intermediate, and long-term goals to gradually bring social rhythms into a tighter, less variable range. The therapist emphasizes the importance of establishing a *regular* schedule, even if the schedule most comfortable to the patient is phase shifted, recognizing that many patients with bipolar disorder prefer to establish routines that include a late night bedtime (e.g., 2 A.M.) and a later awakening time (e.g., 10 A.M.). Long-term goals may consist of encouraging the patient to find a job that allows her or him to keep a more regular schedule (e.g., a job in a movie theater that does not begin until noon). In an effort to regulate rhythms, the therapist will also monitor the frequency and intensity of social interactions and identify connections between mood and activity level. If a patient is depressed, the therapist may encourage the patient to participate in more stimulating activities; if hypomanic, the patient will be encouraged to minimize over-stimulation.

During the course of treatment, the therapist continues to review SRMs. The weekly SRM provides the therapist with the opportunity to review progress toward identified social rhythm goals and address impediments to change. In addition, the SRM is used to help the patient self-monitor for evidence of an exacerbation of the mood disorder. When a patient begins to slip into an episode of mania or depression, changes in sleep and activity levels may be detected on the SRM before the patient is aware of a shift in mood. Thus, the SRM is used both as a measure of therapeutic change and as an ancillary mechanism for monitoring symptoms.

Interpersonal Psychotherapy

In addition to the four classic problem areas of IPT (grief, role transition, interpersonal role dispute, and interpersonal

deficits), in IPSRT, a fifth problem area (grief for the lost healthy self) is added.

Grief. The patient and therapist will choose grief or complicated bereavement as the focal problem area when the current affective episode is linked to the death of an important person in the patient's life. What is unique to bipolar disorder is the fact that so-called graveside or funeral parlor mania is not uncommon and may complicate the bereavement process either because the individual during a manic episode did not grieve at the time of the death or his or her inappropriate manic behavior at the various mourning rituals alienated family members and friends.

Role transition. A *role transition* is defined as a change in one's social role. Examples of a role change include starting a new job, becoming a parent, and graduating from college. Patients with bipolar disorders are especially vulnerable, even in the face of relatively minor perturbations in their environment (Frank et al. 1999), and bipolar illness itself may bring about role transitions. For instance, mania-driven, inappropriate behavior may lead to job loss, and depression-associated social isolation may lead to failed relationships. Paradoxically, the process of achieving mood stability may represent a role transition for many patients. In particular, many patients miss the pleasurable hypomanic episodes associated with more variable mood states. It is important that the therapist help the patient mourn the loss of these episodes, identify their negative consequences, and help the patient find pleasures associated with newfound mood stability.

Grief for the lost healthy self. Individuals with bipolar disorder almost always experience the symbolic loss of the person they would have become were they not afflicted with bipolar disorder. In IPSRT, this is referred to as *grieving the lost healthy self*. Considered a special type of role transition, grieving the lost healthy self involves encouraging patients to talk about limits placed on their life by the illness, lost hopes, and missed opportunities. After mourning these losses, the patient is helped to recognize his or her strengths (rather than focusing on the losses), and gently encouraged to set new, realistic goals.

Interpersonal role dispute. An interpersonal role dispute occurs when nonreciprocal expectations are present in intimate relationships. Role disputes are common sequelae of bipolar disorder. Irritability associated with both depression and mania can contribute to the erosion of close interpersonal relationships. Similarly, protracted social withdrawal associated with bipolar depressions can destroy close relationships. Friends and family members may be perplexed and ultimately vexed by the patient's wild swings in mood and energy states, leading to misunderstandings and ultimately entrenched role disputes.

Interpersonal deficits. Individuals with interpersonal deficits have long histories of unsuccessful relationships. Patients with long-standing bipolar disorder whose illness has destroyed virtually all close relationships may be best characterized as experiencing interpersonal deficits. Irritability, a characteristic of many individuals with bipolar disorder, may contribute to chronically contentious interpersonal relationships, which would also be addressed under the interpersonal deficits problem area.

Although built on the principles of IPT, IPSRT differs from IPT in several respects (Swartz et al. 2002). Firstly, IPT focuses on the links between life events and mood. In IPSRT, life events are viewed not only as sources of mood dysregulation but also as potential triggers of rhythm

disruption. Thus, IPSRT addresses interpersonal problems by means of both IPT strategies and behavioral strategies designed to regulate the social rhythm disruptions associated with the interpersonal problem. In addition, IPT for unipolar depression is a therapy of interpersonal change. The therapist actively encourages the depressed patient to take interpersonal risks and make relatively large changes in their interpersonal circumstances in a brief period of time. By contrast, patients with bipolar disorder may destabilize in the face of relatively minor change (Frank et al. 1999) and are likely to deteriorate in the setting of very stimulating shifts in their interpersonal lives. Therefore, in IPSRT the therapist helps the patient *adapt to change* and *find a healthy balance between spontaneity and stability*. Changes are made gradually, and both therapist and patient remain alert to signs of clinical deterioration in the face of change.

Integrating the Components

IPSRT is organized into three discrete treatment phases (initial, intermediate, and maintenance phases). Within each phase, the components of IPSRT are administered variably, in order to accommodate the specific needs of each patient. The relative emphasis of psychoeducation, social rhythm therapy, and IPT strategies will vary according to the phase of treatment and the acuity of the patient's symptoms.

IPSRT for Adolescents

Adolescents with bipolar disorder show impaired school, family, and social functioning and seem to be more impaired than adolescents with other psychiatric disorders (Lewinsohn et al. 1995). Unfortunately, there has been little research on therapies for adolescents with bipolar disorder. Since adolescence is characterized by major biological, psychological, and social role changes, along with frequently dysregulated sleep and social routines, all of which are especially harmful for adolescents with bipolar disorder and are addressed in IPSRT, an adaptation of the treatment for adolescents (IPSRT-A) is an especially promising intervention (Hlastala and Frank 2006).

IPSRT-A is currently being developed and tested at the University of Washington. The adaptations to IPSRT include increased parent involvement (especially during the education phase of treatment), interpersonal interventions specific to adolescents and based on IPT-A (e.g., an emphasis on interpersonal disputes with parents), changes to the SRM in order to make it more salient to an adolescent population (shorter, and including school and homework categories), and a greater emphasis on psychoeducation (Hlastala and Frank 2006).

Research Findings

Several recent studies have examined the efficacy of IPSRT. The first study, Maintenance Therapies in Bipolar Disorder (MTBD), compared IPSRT with an intensive clinical management approach in patients with bipolar I disorder. The aforementioned STEP-BD trial examined several intensive psychotherapies (including IPSRT) in comparison to a "clinical management" approach among acutely depressed patients with bipolar disorder. Two smaller studies examined the feasibility of using IPSRT as a monotherapy for bipolar II depression.

MTBD, conducted at the University of Pittsburgh, was the first test of IPSRT as a treatment for bipolar disorder (Frank et al. 2005). In MTBD, acutely ill patients whose symptoms met the criteria for bi-

polar I disorder ($N=175$) were treated with medication and randomly assigned to receive either IPSRT or intensive clinical management (ICM).

Frank et al. (2005) reported the 2-year outcomes of the acute and maintenance phases of the MTBD trial. After adjustment for age, sex, marital status, index episode polarity, medical burden, history of anxiety disorder, history of alcohol or substance abuse, and baseline HRSD and Bech-Rafaelson mania scores, participants assigned to IPSRT in the acute treatment phase were found to have gone significantly longer without a new affective episode during the 2-year maintenance phase (hazard ratio [HR]=0.35; $P=0.01$) irrespective of maintenance treatment assignment. Participants in IPSRT also had significantly higher regularity of daily routines at the end of acute treatment ($P<0.001$). Furthermore, ability to increase regularity of daily routines during acute treatment was significantly related to reduced likelihood of recurrence during the maintenance phase ($P=0.05$), demonstrating that social rhythm stabilization mediated positive outcomes (Frank et al. 2005). The results of this study suggest that IPSRT may be most effective if it is initiated during treatment of an acute episode of illness. Perhaps such timing motivates patients to be more open to making the difficult lifestyle changes necessary to achieve social rhythm stability.

The STEP-BD examined, across 13 study sites, 293 depressed participants with either bipolar I or II disorder who agreed to a psychosocial intervention. Participants were randomly assigned to receive one of three intensive psychotherapies consisting of up to thirty 50-minute sessions over 9 months (IPSRT [$n=62$], family focused therapy [FFT; $n=26$], or CBT [$n=75$]) or to a control condition, comprehensive care (CC; $n=130$), which consisted of three 50-minute sessions of psychoeducation. All psychosocial treatments were administered in combination with standardized medication algorithms.

STEP-BD patients receiving intensive psychotherapy had significantly higher year-end recovery rates (64% vs. 52%) and shorter times to recovery than patients in CC (HR=1.47; 95% CI=1.08–2.00; $P=0.013$). Patients in intensive psychotherapy were 1.58 times (SE=0.15) more likely to be clinically well during any study month than those in CC ($P=0.002$). In analyses of the effects of type of intensive treatment on time to recovery, a main effect of treatment group was found (log-rank $\chi^2_3=8.02$, $P=0.046$). Within the 1-year time frame, 65% (40/62) of the IPSRT patients recovered (HR=1.48) in comparison to 51.5% (67/130) of the CC patients. When only those who recovered were considered, median time to recovery was 127.5±76.8 days for IPSRT and 146±80.0 days for CC (Miklowitz et al. 2007b). Patients receiving intensive psychotherapy also had better total functioning, relationship functioning, and life satisfaction scores over 9 months compared with those assigned to CC, even after pretreatment functioning and concurrent depression scores were covaried (Miklowitz et al. 2007a).

IPSRT as Monotherapy

The first study to evaluate IPSRT as monotherapy (i.e., not in combination with medication) was performed at the University of Pittsburgh. Although one would discourage this approach for individuals with bipolar I disorder, IPSRT monotherapy was considered to be a reasonable choice for individuals with bipolar II disorder who, by definition, do not experience full-blown manic episodes and have

reduced likelihood of experiencing psychosis. In order to meet the needs of individuals with bipolar II disorder, minor adaptations were made to IPSRT, including a shift in focus from mania/hypomania prevention to depression treatment; identification of complex and mixed mood states; regulation of stimulation; attenuation of grandiosity; and additional work on emotion regulation (Swartz et al. 2012b). The study sample comprised 17 participants, all of whom met DSM-IV criteria for bipolar II disorder and were currently depressed. Participants received weekly 45 minute sessions of IPSRT psychotherapy for 12 weeks. Fifty-nine percent of participants (10/17) completed the study. By visit 12, 41% (n=7) had responded to IPSRT (defined as at least a 50% reduction in depression scores). Participants showed significant improvements over time in both depression and overall illness severity (Swartz et al. 2009). In a subsequent study, unmedicated individuals (n=25) whose symptoms met DSM-IV criteria for bipolar II disorder and who were currently depressed were randomly assigned to attend weekly sessions of IPSRT (n=14) or receive quetiapine (n=11). Both groups showed statistically significant declines in depression and mania scores over time (for both, P<0.05), but there were no differences in outcomes between groups over 12 weeks in this small study (Swartz et al. 2012a). These findings are provocative, suggesting comparability of medication and IPSRT, but must be interpreted with caution because of the small sample size and relatively low overall response rates (about 28%).

Summary

Research to date suggests that IPSRT successfully promotes rhythm stability and, when used as an acute treatment, leads to decreased likelihood of affective episode recurrence, increased occupational functioning, and quality of life when compared with clinical management interventions. Research also suggests that IPSRT may work well as a monotherapy for a subset of patients with bipolar II depression. Further research is needed to sort out when IPSRT contributes significantly to improvements in symptoms and functioning and when adjunctive clinical management will suffice.

Psychodynamic Psychotherapy

Theoretical Basis and Technique

Psychodynamic psychotherapy requires an understanding that the past is repeating itself in the present in a way that creates difficulties for the patient. Disappointments in current relationships may resonate with early problems with parents and siblings. One way the therapist makes these unconscious repetitions more conscious is to take note of how they emerge in the therapeutic relationship between the patient and the therapist. *Transference* is the unconscious re-creation of past relationships in the present with the therapist—that is, the patient attributes qualities to the therapist that originate with figures from the patient's past. The therapist attends closely to the transference and brings it to the patient's awareness when the patient is able to see the parallels. Therapists must also focus on their own feelings that have been directly induced by the patient's behavior as well as issues from their past that may influence how they see the patient. Such feelings are referred to as *countertransference.* Understanding of the countertransference

helps the therapist to discern problems in relationships that the patient encounters in interactions outside the therapy (Gabbard 2010). Therapists also maintain an awareness of the patient's tendency to resist the effort of the therapist to help. *Resistance* reflects the patient's ambivalence about getting better in treatment. In summary, psychodynamic psychotherapy emphasizes an understanding of unconscious conflict as it manifests itself in life outside the therapy as well as in the therapist-patient relationship as transference, countertransference, and resistance.

Understanding how stressors impact the neurobiological characteristics of a major depressive episode is an essential element of psychodynamic psychotherapy. The therapist explores the underlying meanings that a stressor may have to the patient. For example, stressors involving loss and humiliation are more likely to induce depression than events involving loss alone (Kendler et al. 2003). Stressors involving trauma may reawaken earlier losses or trauma.

As the therapist gains an understanding of the patient's depressive state on the basis of the most applicable theoretical framework, repetitive patterns and unconscious conflicts are interpreted and brought to the patient's attention. The therapist examines the patient's use of defense mechanisms and explores how they may be helpful or detrimental to the patient. The patient's improvement is directly linked to gaining insight into these patterns, conflicts, and defenses.

Familiar themes in relationship patterns are explored. Biological predispositions, as well as intergenerational reenactment patterns, are also considered. Information on early losses or trauma is gathered. The therapist analyzes how these losses or trauma impacts the patient's relational style and overall behavior. Behavioral patterns are observed. Finally, the patient's personality characteristics are assessed to see if they form a predisposing matrix that contributes to the depression. For example, too much perfectionism may make one feel like it is impossible to reach one's goals, leading one to feel hopeless.

Psychodynamic therapy is provided along an expressive-supportive continuum of interventions. At times the patient will need support, and the therapist will focus on empathic validation, advice, and bolstering of adaptive defenses. When the patient is in a more reflective frame of mind, the therapist offers insight and exploration of the interface between what happened in the past and what is currently taking place through interpretation, confrontation, and clarification.

The psychotherapy proceeds by hopefully listening to how patients formulate their experience of depression and stressors, particularly the meanings of the stressors to the patient. One also observes the way the patient relates to the therapist and the narrative of the patient's life that is told in the history taking. Therapists also observe ways that the patient unconsciously resists the therapist's efforts to help, considering the possibility that the patient feels the depression is deserved and he should not get better.

A useful model to formulate the patient's depression is identification of the Core Conflictual Relationship Theme (CCRT), an approach first described by Luborsky (1984). The CCRT, which is often a centerpiece of the patient's depression, takes the form of three interrelated phenomena: 1) the patient's wishes, expectations, or fantasies about others; 2) the perceived reaction of the other person to those wishes, expectations, or fantasies; and 3) the patient's response to the imagined reaction of the other. Therapists

listen for the CCRT in the patient's stories about childhood and adult life, and they also observe the emergence of the CCRT in the therapeutic relationship.

As the psychotherapy proceeds, the psychodynamic therapist interprets and explains unconscious conflicts and patterns within relationships that are repeating themselves in the patient's present situation outside the therapy and in the therapy to help them understand the origins of their depression. The therapist also offers support and empathic validation for the patient's beleaguered self state. In addition, the therapist helps the patient understand defenses and explore how these defenses keep the patient from self-examination.

An example of an interpretation of a CCRT is the following: "After getting to know you, I can see that you always imagined that you had to be perfect to please your dad, but you assumed that nothing you did would ever please him, and he would be disappointed in you. As a result, you gave up and decided not to try anymore." The therapist might also help the patient see how that fantasy plays out in the therapeutic relationship with the assumption that the therapist expects perfection from the patient.

Short-term psychodynamic psychotherapy (STPP) usually consists of 20–24 weekly sessions (Gabbard 2010). Long-term psychodynamic psychotherapy (LTPP) is open-ended and is usually conducted at a frequency of once or twice per week. The indications for longer-term therapy are when brief therapy is not sufficiently effective, particularly when the presence of long-standing personality traits complicates the recovery. The typical duration of brief therapy is 3–6 months unless there are complicated characterological features that require long-term therapy (Leichsenring 2009).

Outcome Studies

Driessen et al. (2013) compared the efficacy of psychodynamic psychotherapy with that of CBT in a randomized controlled trial involving 341 outpatients seeking treatment for major depressive disorder, making it the largest RCT of dynamic psychotherapy ever conducted. Each group received 16 sessions of treatment. No statistically significant treatment differences were found for any of the outcome measures. The average post-treatment remission rate was 22.7%. The key finding was that psychodynamic psychotherapy was not inferior to CBT.

Two meta-analyses, both of which have focused on STPP, confirm the efficacy of psychodynamic psychotherapy for the treatment of depression. In the meta-analysis by Driessen et al. (2010), which included 23 studies totaling 1,365 subjects, STPP was found to be significantly more effective than control conditions, and the changes from pretreatment to posttreatment were large and maintained at follow-ups for up to 1 year. When STPP was compared with other psychotherapies, no significant differences were found at 3-month or 12-month follow-up. Those treatments that focused more on the supportive end of the continuum were equally as effective as those that were more expressive in focus.

Cuijpers et al. (2008) conducted seven meta-analyses involving a total of 53 studies in which seven major types of psychotherapy for mild to moderate adult depression were directly compared with one another. Each major type of treatment had been examined in at least five randomized comparative trials, and psychodynamic psychotherapy was one of the treatments considered. The investigators found no evidence that one of the treatments was more or less efficacious, with

the exception of interpersonal therapy (somewhat more efficacious) and nondirective supportive treatment (somewhat less efficacious). They concluded that there were no large differences in efficacy between the major psychotherapies for mild to moderate depression.

There is also evidence that the effectiveness of short-term psychodynamic psychotherapy is comparable to that of the antidepressant fluoxetine in mild to moderate depression. Salminen et al. (2008) studied 51 patients with major depressive disorder of mild or moderate severity and randomly assigned them to receive either STPP or fluoxetine 20–40 mg/day for 16 weeks. Both treatments were highly effective in reducing symptoms as well as improving functional ability.

A randomized controlled pilot investigation (Gibbons et al. 2012) found that STPP is effective for depression in a community mental health system. Forty treatment-seeking patients with moderate-to-severe depression were randomly assigned to receive 12 weeks of psychotherapy with either a community therapist trained in brief dynamic psychotherapy or a therapist providing treatment-as-usual (TAU).

When the results were examined, it was determined that blind judges were able to discriminate the dynamic sessions from the TAU sessions on adherence to dynamic interventions. Moreover, although this pilot study did not have adequate statistical power to assess efficacy, moderate to large effect sizes in favor of the dynamic psychotherapy over the TAU therapy were noted: 50% of patients treated with dynamic therapy moved into a normative range on depressive symptoms, compared with only 29% of patients treated with TAU.

There is a smaller body of research addressing the value of combining dynamic therapy with medication for major depressive disorder. Maina et al. (2009) compared treatment for major depressive disorder with brief dynamic therapy plus pharmacotherapy to pharmacotherapy alone. The study included a 6-month continuation treatment trial with pharmacotherapy and a prospective naturalistic 48-month follow-up without any treatment. The patients who received combined treatment, in comparison to those who were treated with pharmacotherapy alone, showed a significantly lower rate of recurrences of depressive episodes at 48-month naturalistic follow up. The investigators concluded that adding brief dynamic therapy to medication in the acute phase is an advantage in long-term outcome compared with providing pharmacotherapy alone.

Summary

With the limited data involved, most experts agree that brief dynamic therapy alone is sufficient for mild to moderate depression, but with the presence of neurovegetative symptoms or otherwise more severe depressions, combining psychotherapy with medication may well be a better treatment approach. At the current state of the art, we do not have sufficient data to determine which patient or clinical characteristics are associated with better outcomes from dynamic therapy vs. other therapy. However, Blatt et al. (1995) reanalyzed data from the National Institute of Mental Health Treatment of Depression Collaborative Research Program and found that highly perfectionistic and self-critical patients did not respond well to any of the four treatment cells. Hence, patients with obsessive-compulsive and perfectionistic traits who are unlikely to respond to brief therapy might be good candidates for a longer term approach to therapy.

Family-Based Treatments

Family-based interventions can be especially important when mood disorders arise in the context of family dynamics or communication styles that appear dysfunctional. In major depressive disorder, randomized trials indicate that family psychoeducation about depression is associated with longer time until relapse (Shimazu et al. 2011). From a preventative standpoint, family-based cognitive therapies have been shown to reduce anxiety and depressive symptoms in adolescent offspring of parents with major depression (Compas et al. 2011). Toddler-parent psychotherapies also have been described with offspring of depressed mothers, based on concerns that the development of insecure attachment relationships may contribute to risk for future depression. For adult and adolescent patients with bipolar disorder, a theoretical framework for family based therapy has been a particular focus of interest.

Family Focused Therapy

Family focused therapy (FFT) is an outpatient psychoeducational therapy for bipolar patients and their caregivers (usually, parents or a spouse). It is administered in up to 21 conjoint sessions of psychoeducation, communication training, and problem-solving skills training, usually during the stabilization phases following acute manic, mixed, or depressive episodes. Given in conjunction with pharmacotherapy, FFT has been found to be more effective than brief psychosocial care in hastening recovery from depressive episodes, delaying recurrences and hospitalizations, reducing symptom severity, and enhancing psychosocial functioning over periods of 1–2 years. FFT has been adapted and found to be effective for adolescent patients with bipolar disorder and children or adolescents at high risk for bipolar disorder.

Theoretical Background

FFT was developed from the observation that high levels of *expressed emotion* (EE) in caregivers are associated with poorer outcomes of bipolar and other recurrent psychiatric disorders. "High EE" means that one or more caregivers express a high frequency of critical comments, hostility, and/or high levels of emotional overinvolvement (overprotectiveness, inordinate levels of self-sacrifice for the individual's care); families are characterized as "low-EE" if no caregiver expresses these attitudes. EE is usually assessed from the 1- to 1.5-hour Camberwell Family Interview (Vaughn and Leff 1976). In a meta-analysis of 28 longitudinal studies of EE in schizophrenia, 23 studies replicated the same finding: patients who recover from an illness episode in high-EE family environments are two to three times more likely to relapse in the next 9–12 months than those in which caregivers express more benign, less evaluative or protective attitudes. Several longitudinal studies have found that EE is a predictor of relapse among patients with bipolar disorder and major depression (Honig et al. 1997; Hooley and Teasdale 1989; Miklowitz et al. 1988; O'Connell et al. 1991; Priebe et al. 1989; Yan et al. 2004). The association between EE and severity of symptoms was also found in a 2-year study of adolescents with bipolar disorder undergoing family treatment (Miklowitz et al. 2006).

EE derives in part from caregivers' attitudes about and perceived causes of the patient's illness. High-EE caregivers of the patient with psychiatric illness are more likely to interpret the patient's negative behaviors, such as irritable moods,

depressive withdrawal, lack of motivation, or suspiciousness, as controllable by the patient (see, e.g., Hooley and Licht 1997; Wendel et al. 2000). Second, during the postepisode period, high-EE caregivers and patients are more likely to engage in counterproductive "attack–counterattack" cycles of verbal interaction than are low-EE caregiver/patient pairings (Simoneau et al. 1998). The patient contributes to the affective tone of these interactions, often criticizing his or her relatives as well as responding to criticisms from them (Miklowitz et al. 1998).

These features of the post-episode family environment, while not directly caused by any one person's behavior, have direct implications for family treatment. The family's "affective climate" — such as whether highly critical attitudes of relatives are expressed directly to the patient and lead to negative interactions— is addressed by communication and problem-solving skill training in FFT. Second, helping caregivers distinguish what behaviors of the patient can and cannot be controlled by him or her—which is not necessarily clear during the post-episode period—is a key component of psychoeducation. The clinician hypothesizes that a parent or spouse will react differently to a patient whose aversive behaviors can be attributable to a brain-based illness, rather than to oppositionality, lack of effort, or negative personality traits.

Structure of FFT

Psychoeducation. FFT begins with between five to seven sessions of psychoeducation, in which caregivers and patients are acquainted with the symptoms of bipolar disorder, cycling patterns, genetic/biological vulnerability and stress, the importance of regular medication treatment and follow-up appointments to manage side effects, risk and protective factors for future episodes, and the potentially protective value of the family. The sessions are conducted in Socractic style. For example, a handout on manic symptoms is passed around, and the patient is told, "You're the expert on this disorder, having gone through it. Can you tell us which of these symptoms you remember having, and what they felt like?" Caregivers are asked to share their own perceptions. The objective is to achieve a consensus on how the patient's most recent episode developed and what stress factors played a role in its onset (e.g., loss of a romantic relationship; an event that changed sleep/wake cycles).

Toward the end of psychoeducation, the family is assisted in developing a relapse prevention plan, consisting of a written summary of warning signs of recurrence, stress triggers, and strategies to use when warning signs first appear. These strategies may include calling the physician to arrange changes in medication (or to reexamine the regimen if the patient has been nonadherent); arranging a hospitalization; or introducing behavioral strategies such as more regular sleep times, reducing the patient's work responsibilities, or sharing parenting duties. If the patient is depressed and suicidal, the relapse plan may include behavioral activation exercises that increase the patient's level of contact with important others and interpersonal communication tasks that increase the patient's perceptions of familial support. If the patient is using substances, the clinician takes a nonjudgmental stance but makes clear the high-risk implications of unresolved manic symptoms, substance misuse, and medication nonadherence.

Communication enhancement training. Approximately 2–3 months into FFT, the patient's initial episode may have stabilized, although many patients continue to have unresolved depression or mixed symptoms. At this point, skill train-

ing that addresses key family dynamics can be undertaken. The second module of FFT, communication enhancement training, lasts 7–10 sessions, depending on the needs of the family and their prior skill levels. This module starts with two assumptions. First, negative family communication reflects distress within the family or couple in the members' attempts to deal with the disorder. The same family may not communicate negatively when the patient is in remission. Second, the frequency of aversive communication under conditions of stress can be reduced through skill acquisition.

Using a behavioral rehearsal format, patients and caregivers learn four communication skills: expressing positive feelings, active listening, making positive requests for changes in others' behaviors, and constructively expressing negative feedback. The first two skills usually generate a feeling of collaboration between members of the couple or family. Then, they may be able to rehearse less confrontational ways of asking for behavioral changes in others. For each skill, the clinician gives participants a handout that lists the skill's components (e.g., for active listening: make eye contact, nod your head, ask clarifying questions, paraphrase what you heard). Then the clinician models the skill for the family. Participants are asked to practice each skill with each other, with coaching and shaping by the clinician. Feedback of other family members is actively solicited (e.g., "I didn't think he was really listening, just going through the motions"; "That time, he nodded more so I felt like he was with me"). The speaker or listener is then asked to try the skill again, until he or she has used it successfully in a dyadic interchange with at least one family member. A homework assignment, in which family members and patients keep a written log of their efforts in using the skills, facilitates generalization of the skills to the home and school or work settings.

Problem solving. By 5–6 months, the patient is usually more fully remitted. At this stage, the patient and caregivers are motivated to address quality-of-life issues that have been disrupted by the illness (e.g., how to help a young adult offspring become more independent; how to address relationship conflicts that have been worsened by the illness). The problem-solving module uses a structured format to help families 1) define specific problems, often by breaking large problems into smaller ones; 2) generate or "brainstorm" solutions; 3) evaluate the advantages and disadvantages of each proposed solution; 4) choose one or more solutions to try in the upcoming week; and 5) develop and troubleshoot an implementation plan. For example, assisting a young woman with bipolar II depression in gaining more independence from her family may start with helping her locate work, which in turn might be narrowed further to "how to write a resume" or "how to locate outdoor jobs that do not involve working with people who might set me off." The solutions may include getting help from one or more family members in constructing the resume, going to an employment agency, practicing interviews, or searching online job sites. The implementation plan usually specifies "who will do what" in the next week and what the family and patient should do if no progress is being made.

The last few sessions of FFT are held monthly and help to consolidate gains made during the treatment. For example, the clinician may review the relapse prevention plans with the family and adjust them if needed. The communication skills may be rehearsed. The patient's need for ongoing psychotropic medications is discussed, as well as his or her

and the family's desires for further psychosocial treatment.

Randomized Trials of FFT With Adults

FFT has been examined in several RCTs. Two trials examined the 21-session protocol in patients who were recruited following an acute manic or depressive episode and maintained on mood-stabilizing medications as outpatients. In the University of Colorado Treatment Outcome Project (Miklowitz et al. 2003), 101 patients were randomly assigned to receive FFT and medications or a brief psychoeducation condition (two sessions) and medications. The combination of FFT and medication was associated with lower frequencies of recurrences and longer delays prior to recurrences over a 2-year period than was the combined use of brief treatment and medication. FFT was also associated with more improvement in depression and mania symptoms and positive affective communication between family members and patients (Miklowitz et al. 2003; Simoneau et al. 1999).

In the University of California, Los Angeles Lithium and Family Management Study, patients were randomly assigned following hospitalization for a manic episode to receive FFT (21 sessions) or individual psychoeducation (21 sessions), both given with best-practice pharmacotherapy (Rea et al. 2003). Thus, this study's design had an advantage over the design of the Colorado study: the inclusion of a comparison condition that had an equivalent level of contact. The effects of FFT on time to relapse were not seen in the first year but did appear in the second year. Notably, rates of rehospitalization in the 1- to 2-year period following the 9-month treatment were 12% in the FFT group and 60% in the individual therapy group; for symptomatic recurrence, the rates were 28% and 60%, respectively. In FFT, patients were less likely to need hospitalization when they did have a symptomatic recurrence than those in individual therapy, possibly because family members learned to spot early warning signs and assist the patient in obtaining changes in medication regimens before a hospitalization was necessary.

Both studies found that the effects of FFT were delayed until at least 6 months after the treatment was begun. Patients and family members may need to absorb the education and skill training exercises into their daily lives before treatment has protective effects above and beyond pharmacotherapy. Future studies should examine whether the changes in family communication observed in the Colorado study precede or follow changes in patients' symptoms.

The STEP-BD Study

As indicated in the discussions of IPSRT and CT, the STEP-BD study included FFT as one of the three randomized treatment arms in comparison with a three-session collaborative care (CC) control condition for patients with bipolar depression (N= 293) followed for up to 9 months. Patients assigned to any of the intensive therapies had higher recovery rates over 1 year (64.4%) and recovered an average of 110 days faster than patients in CC (Miklowitz et al. 2007b). In FFT, 77% of the patients recovered by 1 year; in IPSRT, 65%; in cognitive therapy, 60%, and in CC, 51.5%. Considering only patients who recovered, the median time to recovery in FFT was 103.4±94.1 days, compared with 146.0±80.0 days in CC. Patients in intensive therapy were also 1.58 times more likely to remain stable over 1 year than those receiving CC. Finally, patients in intensive therapy—including those in FFT—had better overall functioning, better relational function-

ing, and higher life satisfaction scores over 9 months than those in CC (Miklowitz et al. 2007b).

The numerical differences between the intensive modalities did not reach statistical significance. The common ingredients of the intensive treatments—teaching strategies to manage mood, identifying and intervening early with prodromal symptoms, enhancing patients' adherence with medication regimen, and working toward resolution of key interpersonal or family problems—may have contributed to more rapid recoveries. Although FFT proved to be a potent treatment in this study, the significance of the results was limited by the finding that only 54% of the STEP-BD patients had families who were accessible and willing to participate in sessions. Family availability appeared to differ across the sites of the study.

As noted in Chapter 13 ("Acute and Maintenance Treatment of Bipolar and Related Disorders") of this volume, depressed-phase STEP-BD patients randomly assigned to receive mood stabilizers with adjunctive antidepressants did not recover faster than patients assigned to receive mood stabilizers with placebo. Thus, STEP-BD showed that psychotherapy is an essential component of treatment to stabilize bipolar depressed patients. Clinicians who have the choice of treating bipolar depressed patients with adjunctive antidepressants or adjunctive psychotherapy may find that the second option is in many cases more effective.

FFT in Early-Onset Bipolar Disorder

FFT for adolescents (FFT-A; Miklowitz et al. 2008) uses the same 21-session structure as FFT for adults but is adjusted for the developmental needs of adolescents (ages 12–18). An RCT of adolescents with bipolar I, II, or not otherwise specified disorder (N=58) conducted across two sites found that over 2 years, adolescent patients in FFT-A recovered more rapidly from depressive symptoms, spent less time depressed, and had less severe depressive symptoms than adolescents who received three sessions of psychoeducation (enhanced care, or EC) (Miklowitz et al. 2008). The effects of FFT-A appeared to be moderated by levels of EE among parents. Specifically, adolescents with high-EE parents showed greater improvement in depressive and manic symptoms over 2 years in FFT-A than in EC; the treatment effects within low-EE families were nonsignificant (Miklowitz et al. 2009).

FFT has also been adapted for children and adolescents (ages 9–17 years) who are at risk for developing bipolar disorder (Miklowitz et al. 2013). These are youths who 1) have a first-degree relative (usually a parent) with bipolar I or II disorder and 2) have significant mood dysregulation and impairment in the form of major depressive disorder, cyclothymic disorder, or bipolar disorder not otherwise specified (BD-NOS; renamed other specified or unspecified bipolar and related disorder in DSM-5). A follow-up of children with BD-NOS and a positive family history of mania found that up to half "converted" to bipolar I or II disorder within 5 years (Axelson et al. 2011).

In a 1-year RCT, 40 children who were at high risk of developing bipolar disorder were randomly assigned to receive a shortened version of FFT (FFT, high-risk version, or FFT-HR), given in 12 sessions over 4 months. Comparison participants received 1–2 sessions of a family education control (Miklowitz et al. 2013). Participants in FFT-HR recovered more rapidly from their initial depressive symptoms, had more weeks in remission over 1 year, and showed greater improvement in hypomania symptoms over

1 year than participants in the education control. As in earlier studies, the magnitude of the treatment effect (i.e., improvement in FFT-HR vs. the comparison group) was greater among high-risk children in high-EE, compared with low-EE, families.

Other Family Intervention Approaches

Other family intervention approaches to pediatric mood disorder have been promising. In a large (N=165) wait-list trial, children with depression or bipolar disorder who were assigned to multifamily psychoeducation groups showed greater improvement over 6 study months than children on a waiting list. When children on the waiting list participated in the multifamily groups 1 year later, they showed a comparable amount of mood improvement (relative to the immediate-treatment group) between 12 and 18 months (Fristad et al. 2009).

A family-focused CBT treatment, commonly referred to as the "Rainbow" program, has been developed for school-age children with bipolar disorder. This model incorporates psychoeducation, cognitive restructuring, mindfulness meditation, and affect regulation strategies (Pavuluri et al. 2004). This 12-session treatment was shown to have positive long-term effects in an open trial; results of an RCT are pending (West and Weinstein 2012; West et al. 2007).

Summary

Family interventions have been shown to be effective adjuncts to pharmacotherapy in the outpatient stabilization and maintenance treatment of bipolar and unipolar disorders. Results of FFT studies have been extended to children and adolescent bipolar patients. Not all patients are regularly in contact with caregivers, and not all want to be in treatment with these caregivers, so individual approaches with comparable effectiveness (e.g., IPSRT) are important alternatives for outpatient stabilization. The comparative cost-effectiveness of different forms of psychotherapy for bipolar and unipolar mood disorders has not been investigated.

Engaging family members in treatment during the post-episode period may have beneficial effects on caregivers as well as patients. One randomized trial found that an adapted version of FFT focused on caregiver health, administered to parents or spouses of adult bipolar patients, was effective in reducing caregivers' own depressive symptoms, and in turn, patients' depressive symptoms (Perlick et al. 2010). A psychoeducation group for caregivers that ran parallel to patients' pharmacological treatments had strong benefits for patients in terms of delaying manic recurrences (Reinares et al. 2008). It is possible that caregivers, when educated about the disorder, assist the patient in maintaining healthy lifestyle habits, staying consistent with drug treatment, and keeping in regular contact with attending psychiatrists, all of which contribute to long-term mood stability.

Group Psychotherapy

Several forms of group psychotherapy have been described for both unipolar and bipolar disorders. Content generally focuses on enhancing medication adherence, increasing awareness of prodromal features, recognizing early episodes, and improving social and work functioning. Most outcome studies have focused on euthymic patients taking a variety of pharmacotherapies, limiting the extent to

which the specific effects of a particular psychotherapy can be parsed from concomitant medications, or nonspecific effects of the intervention. Outcome studies also generally have focused on the success of preventing new episodes (rather than hastening the amelioration of symptoms in a current episode), avoiding hospitalizations or minimizing hospital duration, or improving global functioning. Surprisingly little attention has been paid to psychiatric problems that can be uniquely treated by group psychotherapy (e.g., overcoming social anxieties or interpersonal difficulties; drawing on group support); or outcomes focused on improving coping strategies, lifestyle modifications (e.g., normalizing sleep schedules, avoiding substance misuse), and acquiring better stress management skills. To date, there also have been no published randomized comparisons of outcome after individual- versus group-based psychotherapies, although some naturalistic studies have reported larger effect sizes with individual than group-based cognitive behavioral therapies. Modalities of group psychotherapy for mood disorders include CBT, psychoeducation, and a life goals program.

Cognitive-Behavioral Therapy

Group-based cognitive-behavioral therapies adapt basic CBT concepts in a more didactic format, typically dividing sessions into psychoeducation about the disorder and the role of pharmacology, followed by instruction in cognitive strategies to manage affective episodes, assertiveness training and enhancement of problem-solving skills, and relapse prevention techniques. While initial open trials of group CBT for bipolar disorder have been associated with improved psychosocial functioning, randomized studies have not found significant differences in time until episode recurrence between group-based CBT and treatment as usual (Gomes et al. 2011).

Patient or Caregiver Group Psychoeducation

Psychoeducation per se—that is, providing formal information about illness awareness, medication adherence, detection of prodromes and recurrences, and lifestyle regularity—is a common subcomponent of other psychotherapies (e.g., CBT). Controlled studies that exclusively involve psychoeducation have, as of this writing, revealed the greatest enduring effects of any group treatment; thus, after twenty-one 90-minute weekly sessions, fewer recurrences per patient and longer time until any new mood episode have been observed at 2- and 5-year follow-ups (Colom et al. 2009).

Studies of group psychoeducation for caregivers of individuals with bipolar disorder have examined time until any mood recurrence following usually a briefer (e.g., 12) module of 90-minute group sessions attended by caregivers that focuses on increasing knowledge about bipolar disorder and training in coping skills. Time until any mood episode over 12 months, and time until a recurrent mania/hypomania (but not depressed or mixed episode), were significantly longer for patients whose caregivers had been assigned to the active intervention than for control group subjects (Reinares et al. 2008).

Life Goals Program

Developed by Bauer and colleagues (1998), the Life Goals Program (LGP) for bipolar disorder is a manualized program

involving an initial psychoeducational phase (6 weekly 90-minute sessions) aimed to improve patients' self-management skills and participation in medical model treatment, followed by a second phase of helping participants identify and meet functional status goals. The LGP has been associated with fewer recurrences and improved social relationships over 3-year follow-up (Aubry et al. 2012), as well as improved attitudes about medication and treatment adherence at 6-month, but not at 12-month, follow-up.

Conclusion

A number of distinct evidence-based psychotherapies now exist for both unipolar and bipolar disorders, with demonstrated efficacy both acutely and long-term. Questions remain about when to favor one modality over another for a given patient, how best to integrate complementary elements drawn from diverse forms of psychotherapy, how and when to introduce a psychotherapy relative to pharmacotherapy, and how to identify factors that may suggest the unique value of one approach versus another. On the basis of the specific theoretical underpinnings, the goals of psychotherapy of each model of therapy may fruitfully address components of a mood disorder that reach beyond symptoms (e.g., sleep, energy, appetite) as treatment targets—such as restructured faulty cognitive attitudes and beliefs, altering maladaptive defense mechanisms, and improving family and interpersonal functioning and satisfaction. Pending further empirical observations from studies that address these issues, such decisions must rely on thoughtful clinical judgment based on symptom profiles observed within the context of the therapeutic alliance.

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CHAPTER 13

Acute and Maintenance Treatment of Bipolar and Related Disorders

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Bipolar disorders are common, recurrent, frequently debilitating, and in many instances tragically fatal illnesses, characterized by oscillations in mood, energy, and ability to function (Ketter 2010). In this chapter, we describe approaches to the pharmacotherapy of bipolar and related disorders.

As of early 2014, 13 drugs had U.S. Food and Drug Administration (FDA) indications for one or more phases of bipolar disorders (Table 13–1). Most indications are for acute episodes—with 10 monotherapy and 5 adjunctive therapy (added to lithium or divalproex) approvals for acute mania but only 1 monotherapy, 1 combination therapy, and 1 monotherapy and adjunctive therapy approval for acute bipolar depression. Approvals for bipolar maintenance include 5 monotherapies and 4 adjunctive therapies. The schema in Table 13–1 is generally consistent with the notion that effective acute therapies are important candidates for maintenance treatment. Specifically, six of the seven treatments with approved bipolar maintenance indications also have acute mania indications (with lamotrigine being approved only for maintenance treatment but not for acute treatment). With the sole exception of the approval of quetiapine for acute bipolar depression in patients with both bipolar I disorder and bipolar II disorder, all of the indications in Table 13–1 are only for patients with bipolar I disorder. Only quetiapine has FDA indications for all three—namely, acute mania, acute bipolar depression, and bipolar maintenance.

TABLE 13–1. U.S. Food and Drug Administration–approved treatments for bipolar disorder

Year of approval	Drug
Acute mania	
1970	Lithium[P/A]
1973	Chlorpromazine
1994	Divalproex, divalproex ER (2005)
2000	Olanzapine[A/M, P/A]
2003	Risperidone[A/M, P/A]
2004	Quetiapine, quetiapine XR (2008)[A/M, P/A]
2004	Ziprasidone
2004	Aripiprazole[A/M, P/A]
2004	Carbamazepine ERC
2009	Asenapine[A/M]
Acute bipolar depression	
2003	Olanzapine + fluoxetine combination
2006	Quetiapine, quetiapine XR (2008)
2013	Lurasidone[A/M]
Bipolar maintenance	
1974	Lithium[P/A]
2003	Lamotrigine
2004	Olanzapine
2005	Aripiprazole[A/M, P/A]
2008	Quetiapine, quetiapine XR (adjunct)
2009	Risperidone LAI[A/M]
2009	Ziprasidone (adjunct)

Note. LAI = long-acting injectable formulation.
[A/M]Adjunctive and monotherapy.
[P/A]Pediatric and adult.
Source. Adapted from Ketter and Wang 2010b.

The mood stabilizers lithium, divalproex, lamotrigine, and carbamazepine may be argued to be the foundational pharmacotherapies for bipolar disorders, but second-generation antipsychotics (SGAs) have been increasingly used (Ketter 2010). In addition, antidepressants, other anticonvulsants, and novel therapeutic agents are commonly combined with mood stabilizers and SGAs in clinical settings (Ketter 2010).

Evidence-Based Approach to Treatment: Potential Benefits Versus Harms

Evidence-based treatment of bipolar disorders generally begins with interventions that have demonstrated efficacy and safety/tolerability in adequately sized,

multicenter, randomized, double-blind, placebo-controlled trials (Table 13–1). However, clinical needs commonly exceed the management options supported by FDA indications. In such instances, the next best-established treatments are those supported by at least one adequately sized, randomized, double-blind, placebo-controlled trial.

The potential benefits (therapeutic effects) of treatments for bipolar disorders must be considered in the context of potential harms (adverse effects). In recent years, studies have increasingly quantified potential benefits and harms using number needed to treat (NNT) and number needed to harm (NNH) analyses, respectively. NNT is the expected number of subjects that would need to be treated to yield one additional good outcome (defined, in this chapter, as either response [at least 50% decrease in symptoms] in the acute treatment phases or recurrence prevention in the maintenance treatment phase) compared with a control intervention (Laupacis et al. 1988). For example, the NNT for response is calculated by assessing the reciprocal of the absolute risk reduction (difference in the response rates for a treatment and a control intervention). Thus, if a medication and placebo had response rates of 50% and 25%, respectively, then the NNT for response would be

$$100\%/(50\%-25\%)=100\%/25\%=4$$

That is, four patients would need to be treated to expect to obtain one more response (or recurrence prevention) compared with placebo. Lower NNTs represent better outcomes, with (preferably low) single digits generally representing adequate outcomes in bipolar disorders. FDA-approved treatments for bipolar disorders generally have single-digit NNTs. Alternative treatments worth considering may have NNTs as high as the low teens in the setting of good tolerability and a lack of well-tolerated agents with lower NNTs. NNTs for pharmacotherapeutic agents used in the treatment of bipolar disorders are given in Table 13–2.

All of the approved treatments for bipolar disorders have a least one boxed warning regarding serious adverse effect risks. Although such boxed warnings are clearly important, they do not generally represent the most common adverse effects that cause treatment discontinuation (e.g., sedation, weight gain, akathisia). Harms can be quantified using NNH, which is the number of patients who would have to be treated before one additional patient would be expected to experience an adverse effect compared with a control intervention. The NNH for an adverse effect is calculated by assessing the reciprocal of the absolute risk increase (difference in the adverse effect rates for a treatment and a control intervention). Thus, if a medication and placebo had sedation rates of 40% and 20%, respectively, then the NNH for sedation would be

$$100\%/(40\%-20\%)=100\%/20\%=5$$

That is, five patients would need to be treated to expect to encounter one more with sedation compared with placebo. Higher NNHs represent better outcomes, with double digits generally representing adequate outcomes, depending on the degree of severity of the harm. As treatments more likely to help rather than harm are preferred, we strive for interventions with lower NNT than NNH, with a general goal of having a no more than single-digit NNT (i.e., at least 10% more efficacy than placebo) and an at least double-digit NNH (i.e., no more than 10% increase in risk of adverse effect compared with placebo). The likelihood of being helped or

TABLE 13–2. Potential benefits of bipolar disorder treatments: numbers needed to treat

Medication	Acute mania (monotherapy)	Acute mania (adjunctive)	Acute bipolar depression (monotherapy)	Maintenance (monotherapy)	Maintenance (adjunctive)
Mood stabilizers					
Lithium	4			7	
Divalproex DR, ER	7	5[U]		8[U]	
Carbamazepine ER	4				
Lamotrigine			12[U]	9	
First-generation antipsychotics					
Chlorpromazine	?				
Haloperidol	5[U]	6[U]			
Second-generation antipsychotics					
Olanzapine	5	5	12[U]	3	
Risperidone oral, LAI	4	6		4[LA]	?[LA]
Quetiapine IR, XR	6	8	6	4[U]	4
Ziprasidone	7		148[U]		8
Aripiprazole	5	7	44[U]	6	10
Asenapine	8	8			
Lurasidone			5, 7 (adjunctive)		
Cariprazine	7[U]				
Other					
Olanzapine+fluoxetine			4		
Armodafinil			9[U] (adjunctive)		

Note. **Boldface**=NNTs for approved treatments; ?= data not available; LAI=long-acting injectable formulation.
[LA]Long-acting injectable formulation.
[U]Lacks U.S. FDA approval for that indication.
Source. Adapted from Kotter and Wang 2010b.

harmed (LHH, equal to NNH÷NNT) serves as an integrative measure of the balance between benefits and harms that can be expected with interventions. Higher LHHs indicate greater likelihoods of benefits compared with harms, with LHH>1 suggesting that a given intervention is more likely to help than to harm patients.

Risk management strategies vary markedly among clinicians as well as among patients, so that it is crucial to personalize benefit versus harm assessments. During treatment of severe acute symptoms, a greater need for efficacy (lower NNT) may mitigate the increased risk of adverse effects (lower NNH) of more potent treatments such as SGAs. Alternatively, during treatment of mild acute symptoms or during maintenance treatment, a greater need for tolerability (higher NNH) may mitigate the increased risk of inefficacy (higher NNT) of some more tolerable treatments such as antidepressants or lamotrigine.

Controlled trials support the notion that combination therapies can be more potent than monotherapies both acutely and prophylactically. Thus, it is common to encounter approaches in less urgent situations that start with monotherapy (if appropriate) before proceeding to combination therapy (if necessary).

Treatment of Acute Mania

For much of the 1970s and 1980s, lithium and first-generation antipsychotics were the main treatments for acute mania, but this situation changed as the efficacy limitations of lithium and tolerability limitations of first-generation antipsychotics became more evident, and new treatment options emerged. By the late 1990s, divalproex had overtaken lithium, and in the 2000s, SGAs overtook first-generation antipsychotics, as the main treatments. Thus, since 2000, six SGAs (olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, and asenapine) received monotherapy indications for acute mania, and five of these (olanzapine, risperidone, quetiapine, aripiprazole, and asenapine) also received adjunctive (added to lithium or valproate) indications for acute mania. In 2004 a proprietary beaded, extended-release capsule formulation of carbamazepine, and in 2005 an extended-release formulation of divalproex, received monotherapy indications for acute mania. By early 2014, an additional SGA (cariprazine) had been shown to have efficacy as monotherapy for acute mania in two adequately sized, multicenter, randomized, double-blind, placebo-controlled trials, findings from one of which had been presented at a scientific meeting (Starace et al. 2012).

Whereas DSM-IV (American Psychiatric Association 1994) narrowly defined the construct of "mixed episode" as a full manic episode with a full major depressive episode, arising exclusively in bipolar I disorder, DSM-5 has replaced mixed episodes with the more broadly defined "with mixed features" specifier, which may be applied to not only manic (in bipolar I disorder) but also hypomanic (in bipolar I disorder or bipolar II disorder) or major depressive episodes (in bipolar I disorder, bipolar II disorder, or major depressive disorder) that are accompanied by at least three non-overlapping symptoms of the opposite pole. Few pharmacotherapies have, as yet, been studied specifically to treat coexistent manic/hypomanic and depressive symptoms when both poles are not necessarily of syndromal intensity. However, ziprasidone appears superior to placebo when major depression co-occurs with more

than two manic/hypomanic symptoms (Patkar et al. 2012), while antidepressants have been shown to worsen subsyndromal mania symptoms in the setting of bipolar depression (Frye et al. 2009; Goldberg et al. 2009). Depressive symptoms during syndromal mania have been associated with a better response to divalproex than lithium (Swann et al. 1997). Further treatment approaches to mixed features as conceptualized in DSM-5 (including depressive syndromes during hypomanic episodes) require extrapolation from treatment studies of DSM-IV mixed episodes.

Treatment of Acute Bipolar Depression

Criteria for bipolar depression in DSM-5 remain fundamentally unchanged from DSM-IV, with the exceptions that 1) concomitant subsyndromal mania/hypomania (common in half or more of syndromally depressed bipolar patients [Goldberg et al. 2009]) is now recognized by the mixed features specifier, 2) episodes may also include the specifier "with anxious distress," and 3) a full manic or hypomanic episode emerging during antidepressant treatment and persisting beyond the physiological effect of that treatment is now considered sufficient evidence for a manic or hypomanic episode. Evidence-based treatments for acute bipolar depression are heterogeneous. Only three medications carry FDA-approved indications for acute bipolar depression: quetiapine (NNT=6; at a dosage of 300 mg/day, without evidence of greater antidepressant efficacy at 600 mg/day), olanzapine-fluoxetine combination (NNT=4), and lurasidone as monotherapy (NNT=5) or adjunctive therapy (NNT=7). Registration trials of either the immediate- or extended-release formulations of quetiapine in bipolar depression demonstrate comparable efficacy in both bipolar I and II depression, with or without rapid cycling. Lurasidone also has demonstrated efficacy both as monotherapy and as adjunctive therapy with lithium or divalproex for treating acute bipolar I depression (Loebel et al. 2013a, 2013b). By contrast, studies of other atypical antipsychotics have shown either no advantage over placebo (i.e., aripiprazole [Thase et al. 2008] or ziprasidone [Lombardo et al. 2012; Sachs et al. 2011]) or, at best, only modest efficacy in randomized non-placebo-controlled trials (e.g., risperidone [Nierenberg et al. 2006]), precluding generalizations about antidepressant class effects for SGAs.

The utility of antidepressants has long been controversial in bipolar depression, stemming from concerns about both possible mood destabilization (i.e., induction or exacerbation of mania symptoms, or acceleration of cycling frequency) and lack of demonstrated efficacy as compared with mood stabilizers alone. A meta-analysis involving 7,915 bipolar subjects drawn from 73 published reports found that the overall risk of mania with and without an antidepressant was 12.5% and 7.5%, respectively, indicating a significant (P=0.04) increased (1.7-fold greater) risk of mood destabilization from antidepressants, although the likelihood of its occurrence appears applicable only to a modest minority of bipolar patients (Tondo et al. 2010). Co-administration of antidepressants with antimanic drugs also did not meaningfully mitigate this risk (relative risk=1.73 with antidepressant and 1.76 without antidepressant). This finding was consistent with results from the National Institute of Mental Health Systematic Treatment Enhancement Program for Bi-

polar Disorder (STEP-BD), in which rates of treatment-emergent adverse switch in patients receiving mood stabilizer plus antidepressant (10.1%) and patients receiving mood stabilizer plus placebo (10.7%) were not significantly different (Sachs et al. 2007). Nevertheless, practice guidelines advise against using antidepressants without concomitant antimanic drugs in bipolar I depression. A contrarian view has been expressed by Amsterdam and Shults, who report that in bipolar II depression, antidepressant (fluoxetine) monotherapy is superior to placebo and poses no increased risk for short-term (Amsterdam and Shults 2010a) or long-term (Amsterdam and Shults 2010b) mood destabilization. There appears to be considerable interindividual variation in the efficacy and tolerability of adjunctive antidepressants in bipolar disorder, making their use potentially beneficial for some patients and problematic for others.

Despite unresolved controversies, contemporary studies permit several conclusions to be made about antidepressant use in bipolar depression, including the following:

- Treatment-emergent adverse switch appears higher with tricylic antidepressants than with SSRIs or bupropion, and with venlafaxine than with bupropion.
- Identified patient-specific risk factors for treatment-emergent adverse switch from antidepressants includes bipolar I>bipolar II subtype, recent mania/hypomania, mixed features, history of comorbid substance abuse, and previous history of antidepressant-associated mania/hypomania (Goldberg and Truman 2003).
- Antidepressants lack demonstrated efficacy in rapid-cycling bipolar disorder and may hasten depressive recurrences (Ghaemi et al. 2010).
- Robust acute response to an antidepressant plus mood stabilizer appears associated with a greater long-term likelihood of preventing depression relapse without mood destabilization (Altshuler et al. 2009).

Traditional mood stabilizers alone vary in their antidepressant (vs. antimanic) effects. For example, while lithium has been shown to be superior to placebo in bipolar depression, its effects appear more robust against mania than against depression (Geddes et al. 2004). Similarly, several relatively small placebo-controlled trials suggest greater efficacy with divalproex than with placebo in bipolar depression, but its antimanic value appears greater than its antidepressant value. By contrast, as discussed further later in this chapter, lamotrigine appears to possess more substantial antidepressant than antimanic properties.

Novel Pharmacotherapies

A growing number of novel agents have shown preliminary efficacy and safety for the treatment of bipolar depression.

The low-affinity dopamine transporter inhibitor modafinil (at a mean dosage of 175 mg/day), when added to mood stabilizers ± antidepressants, was well tolerated and yielded significantly greater improvement in depression symptoms than placebo in a preliminary randomized trial (Frye et al. 2007). Its *R*-enantiomer, armodafinil (at a dosage of 150 mg/day) also was superior to placebo for bipolar I depression when added to lithium, divalproex, or an SGA (NNT=9; NNH for adverse effect discontinuation=48) (Ketter et al. 2012).

The novel D_2/D_3 agonist pramipexole was well tolerated and led to significantly greater response rates than placebo (67% vs. 20% and 60% vs. 9%) when

added to mood stabilizers in two proof-of-concept studies (Goldberg et al. 2004; Zarate et al. 2004).

N-methyl-D-aspartate (NMDA) antagonists such as ketamine (0.5 mg/kg intravenously) have demonstrated rapid (within 1 hour), significantly greater improvement compared with placebo, with a moderate effect size in studies of bipolar depression (Diazgranados et al. 2010). Subsequent studies have begun to examine the practicability and longevity of antidepressant response to intravenous or intranasal ketamine, as well as other NMDA receptor antagonists (e.g., oral riluzole 50–200 mg/day) or, possibly, glycine-site partial agonists (e.g., GLYX-13).

Bipolar Maintenance Treatment

After almost 30 years without definitive advances in bipolar maintenance treatments, in the last decade evidence-based maintenance treatment options have expanded substantially. Although lithium monotherapy received the first FDA-approved indication for bipolar maintenance in 1974, in the 1990s divalproex monotherapy (as well as lithium monotherapy), perhaps for methodological reasons, failed to separate from placebo in a controlled bipolar maintenance trial, and carbamazepine, perhaps for economic reasons, was not studied in an adequately powered, multicenter, placebo-controlled bipolar maintenance trial. Studies of mood stabilizer combinations as maintenance therapy are rarer than studies of combinations of a mood stabilizer plus SGA. In a large 24-month pragmatic study, lithium was superior to divalproex both as monotherapy and as adjunctive therapy (Geddes et al. 2010). It was not until 2003 that lamotrigine monotherapy became the first new treatment in 29 years to receive an FDA-approved indication for bipolar maintenance. Subsequently, indications for five SGAs (olanzapine monotherapy, aripiprazole monotherapy and adjunctive therapy, quetiapine adjunctive therapy, risperidone long-acting injectable monotherapy and adjunctive therapy, and ziprasidone adjunctive therapy) were also approved for bipolar maintenance (see Table 13–1).

Most bipolar maintenance therapies have more robust antimanic than antidepressant efficacy (Table 13–3). Important exceptions include lamotrigine, which failed to differ from placebo in primary endpoint analysis in five randomized trials for acute bipolar depression (Calabrese et al. 2008) but was superior to placebo in delaying any recurrent mood episode, with more robust efficacy against recurrent bipolar depression than against mania. Another notable exception is quetiapine, which is the only agent with demonstrated superiority to placebo for acute mania, acute bipolar depression, and bipolar maintenance, and appears to be similarly efficacious, when added to lithium or divalproex, in preventing bipolar depression and mania.

Assessing benefits and harms from bipolar maintenance registration trail data can be challenging, as prior to randomization, patients are commonly openly stabilized on the study medication, which "enriches" the sample for study medication acute efficacy and tolerability. In spite of this limitation, placebo-controlled studies yielded similar potentially useful single-digit (i.e., <10) NNTs in FDA maintenance registration trials (ranging from 3 for olanzapine monotherapy to 9 for lamotrigine monotherapy; and from 4 for quetiapine adjunctive therapy to 10 for aripiprazole adjunctive therapy) (see

TABLE 13–3. Potential benefits of bipolar maintenance: numbers needed to treat

Medication	Study	Episode prevention	Mania prevention	Depression prevention
Mood stabilizers				
Lithium	Goodwin et al. 2004	7	8	49
Divalproex[U]	Bowden et al. 2000	8	22	11
Lamotrigine	Goodwin et al. 2004	9	23	15
Second-generation antipsychotics				
Olanzapine	Tohen et al. 2006	3	5	12
Aripiprazole	Keck et al. 2006	6	6	64
Risperidone LAI	Quiroz et al. 2010	4	4	–26
Quetiapine[U]	Weisler et al. 2011	4	6	9
Aripiprazole + Lithium/ divalproex	Marcus et al. 2011	10	13	44
Quetiapine + Lithium/ divalproex	Vieta et al. 2008; Suppes et al. 2009	4	8	6
Ziprasidone + Lithium/ divalproex	Bowden et al. 2010	8	10	56
Risperidone LAI + Lithium/ divalproex	Macfadden et al. 2009	5	7	16

Note. **Boldface** indicates FDA-approved bipolar maintenance treatment; LAI = long-acting injectable formulation.
[U]Lacks U.S. FDA approval for bipolar maintenance.
Source. Adapted from Ketter and Wang 2010a.

Table 13–3, episode prevention column). However, harm assessment may have been underestimated because harms during the open stabilization phase were not considered. Thus, NNHs for at least 7% weight gain with monotherapy ranged from 8 for olanzapine and aripiprazole to 31 for lamotrigine, yielding relapse prevention:weight gain likelihoods (LHHs) ranging from 1.3 for aripiprazole to 3.6 for lithium. The utility of NNH in such circumstances may be profoundly limited by the fact that adverse effects related to the open stabilization phase were not included. For example, both olanzapine and aripiprazole monotherapy had an NNH for at least 7% weight gain during the randomized phase of 8, but the rate of such weight gain in the open stabilization phase was 35% for olanzapine and not reported (but presumably much lower) for aripiprazole.

Treatment of Rapid-Cycling Bipolar Disorder

Patients with rapid-cycling bipolar disorder (i.e., involving at least four mood episodes per year) commonly struggle with illness with a large depressive component, accompanied by suboptimal efficacy with lithium, divalproex, carbamazepine, and antidepressants. In early studies, rapid cycling appeared to predict lithium resistance (Dunner and Fieve 1974), but subsequent work suggested rapid cycling was associated with resistance to other agents, such as carbamazepine (Okuma 1993) and even divalproex (Calabrese et al. 2005). Antidepressant treatment has been suggested to yield more frequent mood episodes in some studies (Kukopulos et al. 1983; Wehr et al. 1988) but not others (Coryell et al. 1992, 2003). In the latter studies, it was suggested that frequent depressive episodes may lead to more antidepressant administration.

There are very few randomized controlled pharmacotherapy trials in exclusively rapid-cycling patients. A 20-month, double-blind, randomized controlled trial found that lithium monotherapy had similar efficacy to divalproex monotherapy but somewhat poorer tolerability in recently hypomanic or manic patients with rapid-cycling bipolar I disorder or bipolar II disorder (Calabrese et al. 2005). Also, a multicenter, randomized, double-blind, placebo-controlled trial indicated that lamotrigine monotherapy (at a mean dosage of 288 mg/day) may have efficacy in rapid-cycling bipolar II disorder (Calabrese et al. 2000). One small placebo-controlled on-off-on study of antidepressant cessation also found improvement in cycling frequency (Wehr et al. 1988).

In clinical practice, varied combinations of mood stabilizers and SGAs are commonly used, and although providers may strive to avoid adjunctive antidepressants, the common occurrence of treatment-resistant depressive symptoms results in substantial rates of utilization of these agents despite concerns regarding efficacy and tolerability. Novel strategies to treat rapid cycling include suprametabolic thyroid hormone, dihydropyridine calcium channel blockers (e.g., nimodipine, isradipine), and midday phototherapy.

Systematic approaches to the management of rapid cycling bipolar disorder have been advocated. For example, the STEP-BD used a three-stage management pathway (Table 13–4) designed to minimize or eliminate antidepressant exposure, with a focus on mood stabilizers and SGAs, and permitting sufficient time for individual interventions to be assessed (Sachs 2004; Schneck 2006).

Treatment of Special Populations With Bipolar Disorder

Children and Adolescents

Management of bipolar disorder in children and adolescents entails accounting for the effects of normal development, age-related clinical presentations, concurrent psychiatric disorders (e.g., attention-deficit/hyperactivity disorder [ADHD], anxiety disorders, substance use disorders), and age-related differences in the efficacy and tolerability of psychiatric medications (Ketter 2010). For example, youths with bipolar disorder commonly

TABLE 13–4. Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) rapid-cycling management pathway

1. Identify, and minimize or eliminate pro-cycling factors (e.g., antidepressants, stimulants, caffeine, sympathomimetics, steroids, alcohol or substance abuse, medical illnesses, and circadian rhythm disturbance). Gradually taper (approximately 25% per month) antidepressants rather than abruptly discontinue them.
2. If cycling persists, first optimize, and later if necessary add, mood stabilizers (e.g., lithium, lamotrigine, divalproex) and/or second-generation antipsychotics (e.g., olanzapine and aripiprazole), emphasizing agents with evidence of utility in bipolar maintenance treatment. Assess efficacy over approximately 4 months or three cycle lengths, using systematic mood charting. Several iterations may be necessary, yielding two-drug, and even three-drug combinations.
3. If cycling still persists, invoke novel treatments (e.g., levothyroxine, electroconvulsive therapy, nimodipine, omega-3 fatty acids, light therapy) with less evidence than those used in stage 2.

Source. Adapted from Sachs 2004.

experience significantly more weight gain with SGAs than do adults. Furthermore, when working with children and adolescents, clinicians must give additional attention to family environments, parental practices, and educational settings in order to maximize positive outcomes for this population. Patients with earlier-onset bipolar disorder (i.e., onset in childhood and adolescence) typically have more morbidity and poorer outcomes than those with later-onset bipolar disorder. Risperidone, aripiprazole, olanzapine, and quetiapine have FDA-approved indications for pediatric mania monotherapy. Also, aripiprazole has a pediatric mania adjunctive (to lithium or valproate) indication and a pediatric bipolar maintenance monotherapy indication.

Women

Management of bipolar disorder in women entails accounting for the effects of the female reproductive cycle (menarche, menstrual cycle, pregnancy, postpartum period, and menopause), gender-related clinical presentations, concurrent nonpsychiatric medications (e.g., hormonal contraceptives), and gender-related differences in the efficacy and tolerability of psychiatric medications (Freeman et al. 2004; Ketter 2010). The complexity of pharmacotherapy in women with bipolar disorder is increased by the risks of teratogenicity and breastfeeding and drug interactions with hormonal contraceptives.

Older Adults

Management of bipolar disorder in older adults entails accounting for the effects of normal aging, age-related clinical presentations, concurrent medical disorders and related nonpsychiatric medications, and age-related differences in the efficacy and tolerability of psychiatric medications (Ketter 2010; Sajatovic and Blow 2007). Because of tolerability challenges and pharmacokinetic differences, medication doses in older adults, compared with younger adults, are not uncommonly 50% lower. Tolerability limitations of somatic therapies with more side effects (e.g., SGAs) may be particularly important in older adults.

Treatment of Bipolar Disorder and Comorbid Psychiatric Disorders

Patients with bipolar disorder commonly have comorbid psychiatric disorders, which tend to be associated with poorer mood outcomes. Unfortunately, the evidence base regarding the treatment of comorbid psychiatric disorders in patients with bipolar disorder is extremely limited. In some patients, the comorbid disorder(s) may be sufficiently entrained to mood cycling such that stabilizing mood (e.g., with certain mood stabilizers and/or SGAs) will provide sufficient control of the comorbid disorder(s). However, it is common to need to simultaneously treat both the bipolar disorder and the comorbid disorder(s). Because substance use disorders and anxiety disorders represent the most frequent psychiatric comorbidities in bipolar disorder (Kessler 1991), treatments that possess anxiolytic properties without incurring risk for mood destabilization are often key elements of an effective combination pharmacotherapy regimen. Moreover, anxiolytic efficacy bears relevance for addressing presentations described by the DSM-5 specifier "with anxious distress" across all acute illness phases.

The FDA registration trials in bipolar depression of quetiapine (Hirschfeld et al. 2006) and olanzapine-fluoxetine combination (Tohen et al. 2003) included secondary analyses demonstrating reductions in concurrent anxiety symptoms. Clinical trials targeting comorbid anxiety as a primary outcome in bipolar disorder are lacking, prompting the frequent empirical use of adjunctive benzodiazepines, serotonergic antidepressants, and anxiolytic anticonvulsants such as gabapentin. In a study of bipolar disorder with comorbid alcoholism, adjunctive divalproex was superior to placebo plus usual treatment for decreasing heavy drinking over 24 weeks (Salloum et al. 2005). In euthymic bipolar youths with ADHD, a 4-week controlled trial of adjunctive methylphenidate resulted in significant improvement in ADHD symptoms without destabilizing mood (Findling et al. 2007). Patients with bipolar disorder and comorbid Cluster B personality disorders, such as borderline personality disorder, are commonly administered adjunctive psychotherapy such as dialectical behavior therapy (DBT), although, to date, the limited published studies of DBT in patients with bipolar disorder have focused on treatment of the bipolar disorder itself (Van Dijk et al. 2013). As noted above, adjunctive use of anticonvulsants other than divalproex, lamotrigine, or carbamazepine, although generally not effective for bipolar disorder itself, may in some instances be effective for comorbid conditions. Examples include gabapentin/pregabalin for pain or anxiety; topiramate for migraines, obesity, and alcohol abuse; and zonisamide for obesity.

Mood Stabilizers

Lithium

Lithium is an established treatment for acute mania and bipolar maintenance in adults and youths age 12 or older that appears to decrease suicidal behavior and suicide (Baldessarini et al. 2006; Bauer et al. 2006; Jefferson et al. 1987). Lithium has impressive efficacy in classic bipolar disorder (euphoric manias, non–rapid cycling), but appears to be less effective in patients with manic episodes with mixed features, rapid cycling (at least four episodes per year), comorbid substance

abuse, or severe psychotic or secondary manias; in adolescents; and in patients who have had three or more prior episodes. In addition, its utility is limited by adverse effects, which can undermine adherence.

Lithium's narrow therapeutic index requires careful monitoring of central nervous system, cardiovascular, renal, thyroid, and gastrointestinal end-organ effects. Severe lithium intoxication can be fatal. The risk of lithium toxicity is high in patients with significant renal or cardiovascular disease, severe debilitation, dehydration, or sodium depletion, or in those taking diuretics, nonsteroidal anti-inflammatory drugs, or angiotensin converting enzyme (ACE) inhibitors. However, in medically healthy individuals, at dosages of 900 mg/day or less, lithium is usually well tolerated and, on occasion even with low therapeutic serum levels, may yield benefit in milder forms of bipolar disorders or when used as an adjunct to other mood stabilizers, antipsychotics, or antidepressants.

Other warnings include the risk of renal problems such as nephrogenic diabetes insipidus and morphological changes with glomerular and interstitial fibrosis and nephron atrophy with chronic therapy, as well as drug interactions. Patients need to maintain adequate fluid and sodium intake, and caution is indicated in the setting of protracted sweating, diarrhea, infection, and fever. Lithium can also yield thyroid problems.

Weight gain can occur with lithium therapy and can significantly compromise adherence. Acneiform and maculopapular eruptions, psoriasis, and folliculitis can occur with lithium. Lithium can also have adverse cardiac effects, ranging from benign eletrocardiographic T wave morphological changes to clinically significant sinus node dysfunction or sinoatrial block, and onset or aggravation of ventricular irritability. Lithium carries teratogenic risk (FDA pregnancy category D) due to a 1/1000–1/2000 risk for tricuspid valve malformation (Ebstein's anomaly). Extended-release preparations may yield fewer gastrointestinal adverse effects than immediate-release formulations.

In acute (e.g., inpatient) settings, lithium is commonly initiated at a dosage of 600 to 1,200 mg/day taken in two or three divided doses, and the dosage increased as necessary and tolerated every 2–4 days by 300 mg/day, with the final dosage not usually exceeding 1,800 mg/day. Some patients may better tolerate weighting the dosage toward bedtime or even taking the entire daily dose at bedtime. Euthymic or depressed patients tend to tolerate aggressive initiation less well than do manic patients. Thus, in less acute situations, such as the initiation of prophylaxis or adjunctive use, lithium can be started at a dosage of 300–600 mg/day, and the dosage increased as necessary and tolerated, by 300 mg/day every 4–7 days. Thus, lithium target dosages are commonly between 900 and 1,800 mg/day, yielding serum levels from 0.6 to 1.2 mEq/L (0.6–1.2 mM/L), with the higher portion of the range used acutely, and lower doses used in adjunctive therapy or prophylaxis.

Clinical assessments during lithium therapy include a baseline physical examination and routinely querying patients regarding central nervous system (sedation, tremor, ataxia), gastrointestinal (nausea, vomiting, diarrhea), metabolic (weight gain), thyroid (hair loss, cold intolerance), and renal (polyuria, polydipsia) disorders and adverse effects at baseline and during treatment. Laboratory monitoring includes a baseline pregnancy test, electrocardiogram (in patients over age 40), and renal (blood urea nitrogen, serum creatinine and electrolytes) and thyroid (thyroid-stimulat-

ing hormone [TSH]) indices. Annual or semi-annual monitoring of renal and thyroid indices is also indicated. Serum lithium concentrations are commonly assessed at steady state, which occurs at about 5 days after a dosage change, and then as indicated by inefficacy or adverse effects. More frequent laboratory monitoring is prudent in medically ill patients and in patients with abnormal indices.

Divalproex

Divalproex has demonstrated efficacy for acute manic and mixed episodes in adults (age 18 or older). Although a controlled trial of divalproex maintenance therapy in adults failed, perhaps as a result of methodological limitations, divalproex is commonly used for relapse prevention in bipolar disorder (American Psychiatric Association 2002; Suppes et al. 2005), and several SGAs have been FDA-approved for bipolar maintenance treatment combined with divalproex (or lithium).

Teratogenic risk associated with divalproex (FDA pregnancy category D) includes major congenital malformations (notably, neural tube defects) that could arise more often than with lamotrigine, carbamazepine, or no anticonvulsant exposure. Other significant adverse effects can include pancreatitis, hyperammonemic encephalopathy in patients with urea cycle disorders, somnolence in older adults, thrombocytopenia, hypothermia, multi-organ hypersensitivity reactions, and suicidality (an anticonvulsant class warning). Divalproex therapy has also been associated with polycystic ovary syndrome (PCOS).

Common, dose-related adverse effects with divalproex include gastrointestinal (nausea, vomiting, dyspepsia, diarrhea), hepatic (transaminase elevations), central nervous system (tremor, sedation, dizziness), and metabolic (weight gain, osteoporosis) problems, and hair loss. Central nervous system adverse effects may be attenuated by weighting dosage toward bedtime or dosage reduction, and the divalproex extended-release may yield fewer gastrointestinal side effects than the delayed-release formulation, while the delayed-release formulation in turn may be better tolerated than valproic acid.

In acute settings, such as the inpatient treatment of mania, divalproex in the past was commonly initiated at a dosage of 750–2,000 mg/day, and dosage increased as necessary and tolerated, by 250 mg/day every 1–2 days. Subsequent studies described more aggressive oral loading in acute mania, with the dosage initiated at 20–30 mg/kg. However, euthymic or depressed patients tend to tolerate aggressive initiation less well than manic patients. Thus, in less acute situations, such as when prophylaxis or adjunctive use is being initiated, divalproex is often started at a dosage of 250–500 mg/day, and the dosage increased as necessary and tolerated, by 250 mg/day every 4–7 days. Target dosages in the past were commonly between 750 and 2,500 mg/day, yielding, in earlier studies, serum levels between 50 and 125 μg/mL (350–850 μM/L), with the higher portion of the range used acutely, and lower doses used in adjunctive therapy or prophylaxis. However, in a more recent acute mania study with divalproex extended-release formulation, target serum levels ranged from 85 to 125 μg/mL (600–850 μM/L).

Divalproex inhibits hepatic metabolism and thus can increase serum concentrations of other medications, such as lamotrigine, carbamazepine epoxide, and the anticonvulsants ethosuximide, felbamate, phenobarbital, and phenytoin. Also, hepatic enzyme-inducers such as

the anticonvulsants carbamazepine, phenobarbital, and phenytoin can decrease valproate serum concentrations. Clinical assessments include a baseline physical examination and periodic monitoring of weight as well as of hepatic, neurological, and hematological effects. Laboratory monitoring during divalproex therapy commonly includes baseline complete blood count, differential, platelets, and hepatic indices, and reevaluation every 6–12 months and as clinically indicated. Serum valproate concentrations are typically assessed at steady state and then as clinically indicated by inefficacy or adverse effects.

Lamotrigine

Lamotrigine is approved for bipolar maintenance treatment in adults (age 18 or older), and is generally well tolerated, particularly in comparison to other treatment options. The most common adverse events in bipolar disorder patients in clinical trials were headache, benign rash, dizziness, diarrhea, dream abnormality, and pruritus.

Lamotrigine carries a manufacturer's "black box" warning regarding the risk of serious rashes requiring hospitalization, which have included Stevens-Johnson syndrome. The risk of rash is higher in patients younger than 16 years, during coadministration with divalproex, and if the recommended initial lamotrigine dose or dosing escalation is exceeded. Benign rash may be seen in 10% of patients, but because any rash is potentially serious, any rash requires evaluation and drug discontinuation unless it is clearly not drug related. Other warnings in the prescribing information include the risks of suicidality (an anticonvulsant class warning); hypersensitivity reactions (with fever and lymphadenopathy, but not necessarily rash); acute multiorgan failure; blood dyscrasia; aseptic meningitis; risk of medication errors (confusion with other medications); lower and higher lamotrigine serum concentrations when given with hormonal contraceptives and divalproex, respectively; binding in the eye and other melanin-containing tissues; and withdrawal seizures in bipolar disorder patients, so that unless safety concerns demand abrupt discontinuation, lamotrigine should be tapered over 2 weeks.

Lamotrigine can cause central nervous system (headache, somnolence, insomnia, dizziness, tremor) and gastrointestinal (nausea, diarrhea) adverse effects. In most instances these problems attenuate or resolve with time or lamotrigine dosage adjustment but in occasional patients may require lamotrigine discontinuation. Unlike other mood stabilizers, lamotrigine has not been associated with weight gain.

Lamotrigine dosage is initially titrated *very slowly* in order to decrease the risk of rash. When lamotrigine is given without valproate, the prescribing information recommends starting lamotrigine at 25 mg/day for 2 weeks, then increasing the dosage to 50 mg/day for the next 2 weeks, then increasing to 100 mg/day for 1 week, and then increasing to 200 mg/day in a single daily dose, with dosages exceeding 200 mg/day not recommended unless concurrent hormonal contraceptives (which decrease serum lamotrigine concentrations) are administered. Nevertheless, even in the absence of a hormonal contraceptive, selected patients may benefit from further gradual lamotrigine titration to final dosages as high as 400–500 mg/day.

When lamotrigine is added to divalproex, recommended doses are halved, so lamotrigine is started at 25 mg every other day (although 12.5 mg/day may

be worth considering) for 2 weeks. Then the dosage is increased to 25 mg/day for the next 2 weeks, then increased to 50 mg/day for 1 week, and then increased to 100 mg/day in a single daily dose, with dosages exceeding 100 mg/day not recommended unless concurrent hormonal contraceptives (which decrease serum lamotrigine concentrations) are administered. Nevertheless, even in the absence of hormonal contraceptive, selected patients concurrently taking divalproex may benefit from further gradual lamotrigine titration to final dosages as high as 250 mg/day.

When lamotrigine is given with carbamazepine, doses may be doubled, so that lamotrigine may be started at 50 mg/day for 2 weeks, then the dosage increased to 100 mg/day for the next 2 weeks, then increased to 300 mg/day for 1 week, and then increased to 400 mg/day in divided doses, with dosages exceeding 400 mg/day not recommended unless concurrent hormonal contraceptives (which decrease serum lamotrigine concentrations) are administered. Nevertheless, even in the absence of hormonal contraceptive, selected patients concurrently taking carbamazepine may benefit from further gradual lamotrigine titration to final dosages as high as 800 mg/day.

Patients should be advised that if they fail to take lamotrigine for five half-lives (e.g., approximately 5 days in the absence of carbamazepine, or 3 days in the presence of carbamazepine), gradual reintroduction as described above is necessary, as rashes have been reported with rapid reintroduction.

Patients need to be advised of lamotrigine adverse effects and drug interactions. Clinical assessments with lamotrigine therapy include a baseline physical examination and routinely querying patients regarding rash at baseline and during treatment. Lamotrigine is generally well tolerated, and serum concentrations have not been related to therapeutic effects in patients with bipolar disorder, so therapeutic drug monitoring with lamotrigine is not generally performed.

Carbamazepine

Carbamazepine has demonstrated efficacy for acute manic and mixed episodes in adults (age 18 or older), but complexity of use (related to drug interactions and side effects) and lack of a maintenance treatment indication make it less commonly used than other mood stabilizers.

Carbamazepine therapy is associated with common, benign, as well as rare, serious, adverse events. The most common dose-related adverse effects with carbamazepine involve central nervous system (diplopia, blurred vision, fatigue, sedation, dizziness, and ataxia) or gastrointestinal system (nausea, vomiting) problems. Gradual initial dosing and careful attention to potential drug-drug interactions can help attenuate such problems.

The U.S. carbamazepine prescribing information includes boxed warnings regarding the risks of serious dermatological reactions in individuals with the HLA-B*1502 allele (Asian patients should be genetically tested and, if HLA-B*1502 positive, should not be treated with carbamazepine unless benefit clearly outweighs risk), as well as aplastic anemia (16 per million patient-years) and agranulocytosis (48 per million patient-years). Other warnings in the prescribing information include the risks of teratogenicity, increased intraocular pressure due to mild anticholinergic activity, and suicidality (an anticonvulsant class warning). Thus, carbamazepine can yield hematological (benign leukopenia, benign thrombocytopenia), dermatological (benign rash), electrolyte (asymptomatic hyponatremia), and hepatic (benign trans-

aminase elevations) problems. Much less commonly, carbamazepine can yield analogous serious problems. Rash presenting with systemic illness, or involvement of the eyes, mouth, or bladder (dysuria), constitutes a medical emergency, and carbamazepine ought to be immediately discontinued and the patient assessed emergently.

Although carbamazepine can cause modest increases in TSH levels, frank hypothyroidism is very uncommon. Carbamazepine may affect cardiac conduction and should be used with caution in patients with cardiac disorders. Carbamazepine appears less likely than lithium or valproate to yield weight gain. Carbamazepine-induced hyponatremia is often tolerated in young physically well individuals but can yield obtundation and other serious sequelae in medically frail older adults. Carbamazepine entails teratogenic risk, including risk of neural tube defects (FDA pregnancy category D).

In acute settings, such as the inpatient treatment of mania, carbamazepine therapy is commonly initiated at 200–400 mg/day, and the dosage increased as necessary and tolerated by 200 mg/day every 2–4 days. Euthymic or depressed patients tend to tolerate aggressive initiation less well than manic patients. Thus, in less acute situations, such as the initiation of prophylaxis or adjunctive use, carbamazepine is often started at a dosage of 100–200 mg/day, and the dosage increased as necessary and tolerated, by 200 mg/day every 4–7 days. Even this gradual initiation may cause adverse effects. Thus, starting with 50 mg (half of a chewable 100-mg tablet) at bedtime and increasing the dosage by 50 mg every 4 days can yield a better tolerated initiation. Because of metabolic autoinduction, doses after 2–4 weeks of therapy may need to be twice as high as in the first week to yield comparable serum levels. Target dosages are commonly between 600 and 1,200 mg/day, yielding serum levels from 6 to 12 μg/mL (20–60 μM/L), with the higher portion of the range used acutely, and lower doses used in prophylaxis or adjunctive therapy.

Carbamazepine has multiple problematic drug-drug interactions (in excess of those seen with lithium or divalproex), which are predominantly related to its being a potent hepatic inducer that can decrease serum concentrations and efficacy of psychotropic (including divalproex, lamotrigine, most SGAs, and multiple antidepressants and anxiolytics) and nonpsychotropic medications, and the ability of certain enzyme inhibitors to increase carbamazepine serum concentrations and yield toxicity.

Patients need to be advised of carbamazepine adverse effects and drug interactions. Clinical assessments with carbamazepine therapy include a baseline physical examination and routinely querying patients regarding hepatic and hematological disorders and adverse effects at baseline and during treatment. In the past, recommended laboratory monitoring during carbamazepine therapy has included baseline complete blood count, differential, platelets, hepatic indices, and serum sodium, with re-evaluation at 2, 4, 6, and 8 weeks, and then every 3 months, and as clinically indicated. In contemporary clinical practice, somewhat less focus is placed on scheduled monitoring, whereas clinically indicated (e.g., when a patient becomes ill with a fever) monitoring is emphasized. Patients who have abnormal or marginal indices at any point merit carefully scheduled and clinically indicated monitoring. Serum carbamazepine concentrations have not been established in association with psychotropic efficacy.

Second-Generation Antipsychotics

On the basis of their efficacy profiles and the lower risks of extrapyramidal symptoms and tardive dyskinesia, second-generation antipsychotics have displaced first-generation antipsychotics in the management of bipolar and related disorders. In addition to the aforementioned efficacy of most SGAs in acute mania and bipolar maintenance treatment, and a few SGAs in the treatment of acute bipolar depression, controlled trials suggest the efficacy of cariprazine in acute mania, while clozapine may be effective in patients with treatment-refractory conditions. Short-acting injectable formulations of SGAs such as olanzapine, ziprasidone, and aripiprazole appear useful in the treatment of agitation, and a long-acting injectable (depot) formulation of risperidone may prove useful in bipolar disorder patients with poor medication adherence.

SGAs entail more safety and tolerability challenges than mood stabilizers (e.g., weight gain, metabolic dysregulation, extrapyramidal symptoms, hyperprolactinemia, and sedation), which can attenuate their clinical utility.

Olanzapine

Acute mania dosing recommendations for olanzapine in adult monotherapy include initiating at 10–15 mg once daily and titrating the dose by 5-mg increments as necessary and tolerated to as high as 20 mg once daily. For adult adjunctive (added to lithium or divalproex) therapy, olanzapine is initiated at 10 mg once daily, and the dose is titrated as necessary and tolerated to as high as 20 mg once daily. Acute mania dosing recommendations for olanzapine in adolescent monotherapy include initiating at 2.5–5 mg once daily and titrating by 2.5- to 5-mg increments as necessary and tolerated, with a target dose of 10 mg once daily. Acute bipolar depression dosing recommendations for olanzapine plus fluoxetine in adults include initiating olanzapine at 5 mg and fluoxetine at 20 mg once daily, and titrating the dose as necessary and tolerated within the dosage ranges of olanzapine 5–12.5 mg/day and fluoxetine 20–50 mg/day. It is generally recommended that patients responding to olanzapine continue to take olanzapine beyond the acute response, but at the lowest dose needed to maintain remission.

The most common adverse reactions in adult acute mania trials with oral olanzapine monotherapy were somnolence (35% vs. 13% with placebo; NNH=5), dry mouth (22% vs. 7% with placebo; NNH=7), and dizziness (18% vs. 6% with placebo; NNH=9). In 13 placebo-controlled adult olanzapine monotherapy studies with 8-week median exposure, at least 7% weight gain was seen in 22.2% of patients versus 3% of control subjects receiving placebo (NNH=6). In long-term adult olanzapine monotherapy studies, at least 7% weight gain was seen in 64% of patients. Weight gain appears even more problematic in adolescents than in adults. In placebo-controlled adolescent acute monotherapy studies with olanzapine, at least 7% weight gain was seen in 40.6% of patients versus 9.8% of the placebo group (NNH=4). In long-term adolescent olanzapine monotherapy studies, at least 7% weight gain was seen in 89% of patients. Thus, olanzapine can yield weight gain, diabetes, and hyperlipidemia, with the risk (as with clozapine) being greater than with other SGAs (American Diabetes Association et al. 2004). Somnolence is the most common adverse effect with intramuscular olanzapine. Maximal dosing of intramuscular olanzapine may yield substantial orthostatic hypotension, so that administra-

tion of additional doses to patients with clinically significant postural changes in systolic blood pressure is not recommended. Long-acting injectable olanzapine, although approved for the treatment of schizophrenia, is not approved for the treatment of bipolar disorder.

Risperidone

Risperidone dosing recommendations for acute mania in adults include initiating risperidone at 2–3 mg daily, with the dose increased by 1 mg daily to as high as 6 mg daily. For acute mania in children and adolescents, it is recommended that risperidone be initiated at 0.5 mg daily, with the dose increased by 0.5–1 mg daily to as high as 2.5 mg daily. In order to limit adverse effects, risperidone in bipolar disorder patients who are not manic may be started at 0.25–0.5 mg/day, and the dosage increased as necessary and tolerated every 4–7 days by 0.25–0.5 mg/day, with an initial target dosage of 1–2 mg/day. In bipolar disorder patients, risperidone is often administered all or mostly at bedtime, and commonly in combination with other medications. Once the tolerability of oral risperidone has been established, long-acting injectable risperidone is initiated at 25 mg intramuscularly every 2 weeks, with doses eventually as high as 50 mg intramuscularly every 2 weeks yielding benefit in some patients.

Common adverse reactions in adult acute mania trials with risperidone monotherapy at dosages up to 6 mg/day were parkinsonism (25% vs. 9% with placebo; NNH=7), akathisia (9% vs. 3% with placebo; NNH=17), and sedation (6% vs. 2% with placebo; NNH=25). At least 7% weight gain was seen in 8.7% of patients receiving risperidone at dosages up to 8 mg/day (vs. 2.9% with placebo; NNH=18) and in 20.9% of patients receiving risperidone at dosages over 8 mg/day (vs. 2.9% with placebo; NNH=6) in adult acute mania/schizophrenia trials, and in 32.6% of patients receiving risperidone at dosages up to 6 mg daily (vs. 6.9% with placebo; NNH=4) in pediatric acute mania, schizophrenia, and autism trials. Common adverse reactions in risperidone long-acting injectable bipolar maintenance trials included weight gain (5% in a monotherapy trial), tremor, and parkinsonism (≥10% in an adjunctive therapy trial). Thus, risperidone, like other SGAs, can yield weight gain, diabetes, and hyperlipidemia, with the risk considered intermediate—less than with clozapine and olanzapine, but more than with ziprasidone and aripiprazole (American Diabetes Association et al. 2004).

Quetiapine

Quetiapine acute mania dosing recommendations for adults include initiating quetiapine at 100 mg/day on day 1, then increasing the dosage to 200 mg/day on day 2, 300 mg/day on day 3, and 400 mg/day on day 4, and further increasing the dosage by no more than 200 mg/day to as high as 800 mg/day by day 6. For children and adolescents with acute mania, quetiapine dosing recommendations include initiating quetiapine at 50 mg/day on day 1, then increasing the dosage to 100 mg/day on day 2, 200 mg/day on day 3, 300 mg/day on day 4, and 400 mg/day on day 5, and further increasing the dosage by no more than 100 mg/day to as high as 600 mg/day. Quetiapine acute bipolar depression dosing recommendations for adults include initiating quetiapine at 50 mg at bedtime on day 1, then increasing the dosage to 100 mg at bedtime on day 2, 200 mg at bedtime on day 3, and 300 mg at bedtime on day 4. The recommended dosage of adjunctive (added to lithium or valproate) quetia-

pine for bipolar maintenance in adults is 400–800 mg/day, with the patient generally continuing to take quetiapine at the same dosage that yielded acute mood stabilization.

The most common adverse reactions in adult acute mania and schizophrenia trials with quetiapine monotherapy were somnolence (18% vs. 8% with placebo; NNH=10) and at least 7% weight gain (21.1% vs. 6.6% with placebo; NNH =7). In a pediatric acute mania trial, quetiapine monotherapy yielded at least 7% weight gain in 11.5% of patients versus 0.0% of subjects receiving placebo (NNH=9). In a 26-week pediatric open follow-up study, quetiapine monotherapy yielded at least 7% weight gain in 45% of patients. Thus, quetiapine can yield weight gain, diabetes, and hyperlipidemia, with the risk considered intermediate—less than with clozapine and olanzapine but more than with ziprasidone and aripiprazole (American Diabetes Association et al. 2004).

Ziprasidone

Ziprasidone acute mania dosing recommendations for adult monotherapy include initiating ziprasidone at 40 mg twice daily with food, then increasing the dosage to 60–80 mg twice daily with food on day 2 and titrating as necessary and tolerated to a dosage as high as 40–80 mg twice daily with food. Ziprasidone adjunctive (added to lithium or divalproex) bipolar maintenance recommendations for adults include continuing ziprasidone at the same dosage that yielded mood stabilization, within the range of 40 to 80 mg twice daily. In clinical practice, lower (e.g., less than 80 mg/day) compared with higher (e.g., at least 80 mg/day) dosages of ziprasidone may increase the risk of akathisia, so that optimal titration of this agent may involve avoiding lower doses to prevent akathisia or abruptly increasing to higher doses if akathisia develops at lower doses. Also, for convenience, and in view of the risk of sedation, dosing may be weighted toward dinnertime or bedtime with a snack. Intramuscular ziprasidone for agitation in schizophrenia is administered as 10 mg, with 10 mg intramuscularly repeated as often as every 2 hours as necessary and tolerated, with a maximum of 40 mg/day for 3 days.

The most common adverse reactions in adult acute mania trials with oral ziprasidone monotherapy were somnolence and extrapyramidal symptoms (both 31% vs. 12% with placebo; NNH=6). The most common adverse reaction in an adjunctive (added to lithium or valproate) maintenance trial was tremor. The most common adverse events with intramuscular ziprasidone for agitation in schizophrenia patients were headache, nausea, and somnolence. Ziprasidone, unlike other SGAs, *lacks* warnings/precautions regarding weight gain and, along with asenapine, hyperlipidemia/dyslipidemia. Indeed, the report of a consensus development conference suggested the risks of obesity, diabetes, and hyperlipidemia with ziprasidone were similar to those with aripiprazole, and less than with other SGAs (American Diabetes Association et al. 2004).

Aripiprazole

Aripiprazole acute mania dosing recommendations for adult monotherapy include initiating aripiprazole at 15 mg once daily, with a recommended dose of 15 mg once daily and a maximum dose of 30 mg once daily; for adult adjunctive (added to lithium or valproate) therapy, initiating at 10–15 mg once daily, with a recommended dose of 15 mg once daily and a maximum dose of 30 mg once daily; and for pediatric monotherapy or adjunc-

tive therapy, initiating at 2 mg once daily, with a recommended dose of 10 mg once daily and a maximum dose of 30 mg once daily. In early adult acute mania trials, the mean final aripiprazole dose was approximately 28 mg/day. For aripiprazole monotherapy and adjunctive (added to lithium or valproate) maintenance, it is recommended that aripiprazole be taken at the same dose that yielded acute mood stabilization. In monotherapy maintenance treatment for bipolar I disorder, oral aripiprazole final doses averaged approximately 24 mg/day. In two negative acute bipolar I nonpsychotic depression studies (Thase et al. 2008), aripiprazole monotherapy was initiated at 10 mg/day, and aripiprazole was flexibly dosed within a range of 5 to 30 mg/day, with a pooled mean dose of 16.5 mg/day. Citing high discontinuation rates, the authors speculated that this dosing may have been too aggressive for acute bipolar depression. Indeed, dosing recommendations for adjunctive (added to antidepressants) aripiprazole treatment of unipolar major depressive disorder include initiating aripiprazole at 2–5 mg once daily and titrating to a recommended dose of 5–10 mg/day, with a maximum dose of 15 mg once daily. It may be that the latter, more conservative dosing would be better tolerated in depressed or euthymic bipolar disorder patients. Intramuscular aripiprazole is recommended to be administered as a 9.75-mg intramuscular injection, or a 5.25-mg intramuscular injection if clinically indicated, repeating 9.75 mg (or 5.25 mg) intramuscular injections as often as every 2 hours as necessary and tolerated, with a maximum of 30 mg/day. The prescribing information does not recommend 15-mg intramuscular injections because of concerns regarding adverse effects and the lack of additional benefit with doses over 9.75 mg per injection in clinical trials.

The most common adverse reactions in adult acute mania trials with oral aripiprazole monotherapy were akathisia (13% vs. 4% with placebo; NNH=12) and sedation (8% vs. 3% with placebo; NNH=20). Aripiprazole-related akathisia, like ziprasidone-related akathisia, may respond to benzodiazepines. In adult acute mania trials, oral aripiprazole monotherapy yielded at least 7% weight gain in 2.2% of patients vs. 2.7% with placebo (NNH=–200). The most common adverse reactions in pediatric acute mania trials with oral aripiprazole monotherapy included somnolence (23% vs. 3% with placebo; NNH = 5) and extrapyramidal symptoms (20% vs. 3% with placebo; NNH=6). In pediatric acute mania and schizophrenia trials, oral aripiprazole monotherapy yielded at least 7% weight gain in 5.2% of patients vs. 1.6% of subjects receiving placebo (NNH=28). In open-label extensions of adolescent schizophrenia and pediatric bipolar disorder, 32.8% gained at least 7% weight. The report of a consensus development conference suggested that the risks of obesity, diabetes, and hyperlipidemia with aripiprazole were similar to those with ziprasidone and less than those with other SGAs (American Diabetes Association et al. 2004).

Gastrointestinal adverse effects, such as nausea, dyspepsia, vomiting, constipation, and diarrhea, may be related to dopamine partial agonist effects and tend to diminish with ongoing exposure. Although in view of its long half-life, aripiprazole can be dosed once daily, during the first few days of treatment, the lower maximum concentrations associated with divided doses may offer enhanced tolerability.

Asenapine

Asenapine acute mania dosing recommendations for adult monotherapy in-

clude initiating asenapine at 10 mg sublingually twice daily, which is also the maximum dosage, with the recommended dosage being 5–10 mg twice daily. Dosing recommendations for adjunctive (added to lithium or valproate) asenapine acute mania involve initiating asenapine at 5 mg sublingually twice daily, with a maximum dosage of 10 mg twice daily and a recommended dosage of 5–10 mg twice daily. Asenapine sublingual tablets should be placed under the tongue and left to dissolve completely (which occurs within seconds), and eating and drinking should be avoided for 10 minutes after administration.

The most common adverse reactions in adult acute mania trials with oral asenapine monotherapy were somnolence (24% vs. 6% with placebo; NNH=6) and dizziness (11% vs. 3% with placebo; NNH=13). In adult acute mania trials, asenapine yielded at least 7% weight gain in 5.8% of patients versus 0.5% of subjects receiving placebo (NNH=19). Because of the sublingual route of administration, patients may complain of oral hypoesthesia and/or a bitter taste.

Lurasidone

Lurasidone acute bipolar I depression dosing recommendations for adult monotherapy or adjunctive therapy include initiating lurasidone at 20 mg once daily with food, with a recommended dose of 20–120 mg once daily with food. The most common adverse reactions in adult bipolar I depression trials with lurasidone monotherapy were nausea (14% vs. 8% with placebo, NNH=17), somnolence (11% vs. 7% with placebo, NNH=25), akathisia (9% vs. 2% with placebo, NNH=15), and extrapyramidal symptoms (7% vs. 2% with placebo, NNH=20), and with lurasidone adjunctive therapy, extrapyramidal symptoms (14% vs. 9% with placebo, NNH=20), nausea (14% vs. 10% with placebo, NNH=25), somnolence (11% vs. 5% with placebo, NNH=17), and akathisia (11% vs. 5% with placebo, NNH=17). Lurasidone-related akathisia (like ziprasidone- and aripiprazole-related akathisia) may respond to benzodiazepines. In adult bipolar I depression trials, at least 7% weight gain with lurasidone monotherapy occurred in 2.4% versus 0.7% with placebo (NNH=59), and with lurasidone adjunctive therapy occurred in 3.1% versus 0.3% with placebo (NNH=36).

Lurasidone is a CYP3A4 substrate, so coadministration of lurasidone with strong CYP3A4 inhibitors and inducers is contraindicated.

Cariprazine

Cariprazine (3–12 mg/day; mean dose=7.5 mg/day) has been demonstrated to have monotherapy efficacy in treating acute mania in two adequately sized, multicenter, randomized, double-blind, placebo-controlled trials (Starace et al. 2012). The most common adverse reactions in adult acute mania with cariprazine monotherapy were akathisia (22.8% vs. 4.5% with placebo; NNH=6) and parkinsonism (19.0% vs. 4.0% with placebo; NNH=7).

Additional Adjunctive Interventions in Bipolar Disorder

Diverse additional adjunctive interventions are commonly administered off-label in combination with mood stabilizers and/or SGAs in the clinical management of bipolar disorder. Adjunctive anxiolytics-hypnotics are commonly used in treating bipolar disorder patients to manage

anxiety/insomnia, although for some patients these agents carry a favorable risk-benefit ratio, whereas for other patients the risks of tolerance/withdrawal/abuse may limit the utility of these agents. Randomized trials indicate that anticonvulsants other than divalproex, lamotrigine, and carbamazepine are generally not effective for affective symptoms in bipolar disorder, although some agents may be effective for comorbid conditions, such as gabapentin/pregabalin for pain or anxiety; topiramate for migraines, obesity/binge eating, and alcohol abuse; and zonisamide for obesity. Adjunctive psychotherapies, as described further in Chapter 12 ("Psychotherapy of Mood Disorders"), have demonstrated improved psychosocial outcomes and accelerated time to recovery from bipolar depression. Finally, the use and indications for electroconvulsive therapy and other novel forms of brain stimulation for both unipolar and bipolar disorders are discussed in Chapter 15 ("Brain Stimulation Treatments for Mood Disorders").

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CHAPTER 14

Pharmacological and Somatic Treatments for Major Depressive Disorder

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The American Psychiatric Association (APA) updated their practice guideline for major depressive disorder (MDD) in November 2010. The work group underscored the importance of nonpharmacological aspects of successful treatment that are independent of the actual therapy chosen, including patient-practitioner (the "treatment" or "therapeutic") alliance and use of standardized depression measures such as the clinician-administered Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg 1979) and the self-reported Beck Depression Inventory (BDI; Beck et al. 1961) or Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR; Trivedi et al. 2004) to systematically monitor treatment response over time. After these parameters are established, standard treatment options for unipolar depression include antidepressant medications and/or evidence-based psychotherapy. The choice between medication or talk

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therapy is typically based on patient preference and/or psychiatrist/therapist orientation, because there is a dearth of personalized treatment strategies based on etiopathogenesis of illness. Development of such strategies is certainly a critical future goal, which will be elaborated on later in this chapter.

In this chapter we take a historical perspective of pharmacological and other somatic treatments for MDD by discussing the first-generation of antidepressant medications, the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). We then discuss the discovery and use of the second-generation of antidepressants—namely, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), and atypical antidepressants. Finally, we discuss recent psychopharmacological advances, currently experimental in nature, for the treatment of unipolar depression, with a particular emphasis on developing novel mechanistic approaches, more rapid onset of action, or more sustained symptom reduction or maintenance therapy than provided by currently available antidepressants.

First-Generation Antidepressants

The first-generation antidepressants, TCAs and MAOIs, were discovered serendipitously in the middle of the 20th century. The original TCAs have a chemical structure similar to that of chlorpromazine and, because of their biochemical similarity, were initially studied as potential antipsychotic medications. Although these medications had no benefit on psychosis, they unexpectedly improved mood. The earliest MAOIs, such as iproniazid (related to isoniazid), were developed as antituberculosis drugs, and the antidepressant effects were also discovered inadvertently due to significant improvements in mood independent of any antimicrobial effects.

In addition to this unanticipated antidepressant efficacy, both medication classes share other properties: relatively high side-effect burden and greater risk for lethality in overdose. Nevertheless, these medications are at least as efficacious as newer antidepressants and are often very helpful in treatment-refractory depression (TRD) and chronic pain disorders.

Tricyclic and Related Antidepressants

This class of antidepressants may be divided into the *tricyclic,* referring to the three rings in their structure (e.g., amitriptyline, nortriptyline, clomipramine), and *heterocyclic/atypical,* with a more complex ring structure (e.g., amoxapine, maprotiline). All bind to either the neuronal norepinephrine or serotonin transporter (reuptake site), or, in the case of most, both. Each TCA has differential effects on monoamine reuptake; for example, nortriptyline has greater effects on norepinephrine than on serotonin reuptake, while clomipramine has more effects on serotonin reuptake. Yet, all TCAs inhibit monoamine neurotransmitter reuptake to varying degrees, and this effect is believed to be necessary for their antidepressant properties. Like the specific serotonin reuptake inhibitors to be described below, the antidepressant efficacy lags behind the biochemical effect of monoamine reuptake inhibition, which occurs immediately. TCAs are at least as effective as second-generation (i.e., newer) antidepressants and anxiolytics. Additionally, certain TCAs are prescribed in

low doses for chronic pain syndromes like fibromyalgia and diabetic neuropathy and for sedation in insomnia. They also may be effective in TRD, especially dysthymia and major depression with melancholic features (Perry 1996).

The major differences between TCAs reside in their side-effect profile and lethality risk in overdose. TCAs have anticholinergic, antihistaminic, and anti-α-adrenergic effects, which result, to varying degrees, in the following side effects: 1) blurred vision, dry mouth, constipation, and urinary retention (anticholinergic); 2) sedation and weight gain (antihistaminic); and 3) orthostatic hypotension and tachycardia (anti–α-adrenergic). There are also side effects attributable to the monoamine reuptake properties of these medications. Serotonin reuptake inhibition can produce anxiety, somnolence, nausea, vomiting, diarrhea, or either loss of libido or anorgasmia. Norepinephrine reuptake inhibition can cause anxiety, jitteriness, tachycardia, or insomnia. However, most patients experience fewer and/or less intense side effects with low dose initiation and slow dose titration. Additionally, many side effects abate over time without specific intervention, especially the sedative and gastrointestinal side effects. Another major concern is the potential lethality of TCAs in overdose. All TCAs are cardiotoxic when ingested at supratherapeutic overdoses. Most cause atrioventricular conduction delay, and their anticholinergic and noradrenergic effects may generate lethal arrhythmias. For these reasons and to monitor therapeutic response, many practitioners will monitor serum TCA levels. However, because of concerns about excessive side effects, potential toxicity, and potentially lethal risk in overdose, the newer antidepressants, such as the SSRIs and SNRIs, are often prescribed as first-line pharmacotherapy for MDD (see Table 14–1 for a listing and brief review of the available and most often prescribed TCAs in the United States).

Monoamine Oxidase Inhibitors

MAO is responsible for the intracellular breakdown of serotonin, dopamine, and norepinephrine. Most available MAOIs with antidepressant approval in the United States are irreversible inhibitors of MAO-A (all tissues) and MAO-B (relatively brain-specific). Selegiline is a relatively selective MAO-B inhibitor. MAOIs with an FDA-approved indication for MDD include phenelzine, tranylcypromine, isocarboxazid, and selegiline (transdermal). Like TCAs, MAOIs are typically reserved for TRD and may be especially useful in atypical depression. They are now considered later in a treatment algorithm, not for lack of efficacy, but because of their high side-effect potential, necessary dietary restrictions, serious potential adverse events (such as hypertensive crisis), and possible lethality in overdose. Even though MAOIs can cause hypertensive crises when dietary restrictions are not followed (see below), the most common limiting side effect is actually orthostatic *hypotension.* Other common class side effects are sedation, headache, dizziness, nausea, dry mouth, blurred vision, constipation, and urinary retention.

Tyramine is a naturally occurring dietary monoamine that is taken up into neurons via norepinephrine/epinephrine transporters and displaces norepinephrine and epinephrine. Tyramine is metabolized by MAO, and MAOIs can cause hypertensive reactions in the presence of tyramine-rich foods such as fava beans; a variety of aged foods, including most cheese, cured meats, sauerkraut, marmite, and vegemite, aged fish, and wine; and protein extracts like bean curd

TABLE 14–1. Currently available medications for the treatment of major depressive disorder in the United States

Medication	Preparations/ dosages	Adult starting dosage range (mg/day)	Adult maintenance dosage range (mg/day)	Therapeutic plasma levels (ng/mL)	Cytochrome P450 isozymes affected/ Other features
Selective serotonin reuptake inhibitors (SSRIs)					
Citalopram (Celexa)	T: 10, 20, 40 mg LC: 10 mg/5 mL (generic available)	10–20	20–40		QTc prolongation > 40 mg/day
Escitalopram (Lexapro)	T: 5, 10, 20 mg LC: 5 mg/5 mL (generic available)	5–10	10–20		
Fluoxetine (Prozac, Sarafem)	C: 10, 20, 40 mg LC: 20 mg/5 mL T: 10, 20, 40 mg DR Weekly: 90 mg (generic available)	10–20	20–80		Inhibitor—2D6, 3A4 Longest $t_{1/2}$ of available SSRIs (~2 weeks)
Fluvoxamine (Luvox)	T: 25, 50, 100 mg CR: 100, 150 mg (generic available)	T: 50 CR: 100	100–300		Inhibitor—3A4, 1A2, 2C9/19
Paroxetine (Paxil, Pexeva)	T: 10, 20, 30, 40 mg LC: 10 mg/5 mL CR: 12.5, 25, 37.5 mg (generic available)	T: 10–20 CR: 25	T: 20–50 CR: 25–62.5		Inhibitor—2D6
Sertraline (Zoloft)	T: 25, 50, 100 mg	25–50	50–200		

TABLE 14–1. Currently available medications for the treatment of major depressive disorder in the United States *(continued)*

Medication	Preparations/ dosages	Adult starting dosage range (mg/day)	Adult maintenance dosage range (mg/day)	Therapeutic plasma levels (ng/mL)	Cytochrome P450 isozymes affected/ Other features
Serotonin-norepinephrine reuptake inhibitors (SNRIs)					
Desvenlafaxine (Pristiq)	T: 50, 100 mg	50	50–400		
Duloxetine (Cymbalta)	C: 20, 30, 60 mg	40–60	40–120		Inhibitor—2D6, 1A2
Levomilnacipran ER (Fetzima)	T: 20, 40, 80, 120 mg	40	40–120		Use caution with strong CYP3A4 inhibitor (antifungals)
Venlafaxine (Effexor)	T/C: 25, 37.5, 50, 75, 100 mg XR: 37.5, 75, 150, 225 mg (generic available)	T/C: 75 XR: 37.5	T: 75–375 XR: 225		More serotonergic at low doses, noradrenergic at high doses
Tricyclic antidepressants (TCAs) (generics available for all listed below)					
Amitriptyline (Elavil)	T: 10, 25, 50, 75, 100, 150 mg	50–75	50–300	>120 (?)[a]	
Amoxapine (Asendin)	T: 25, 50, 100, 150 mg	100–150	200–400		
Clomipramine (Anafranil)	C: 25, 50, 75 mg	25	100–250		Most serotonergic of TCAs
Desipramine (Norpamin)	T: 10, 25, 50, 75, 100, 150 mg	25–75	100–300	>125	
Doxepin (Adapin, Sin					

TABLE 14–1. Currently available medications for the treatment of major depressive disorder in the United States *(continued)*

Medication	Preparations/ dosages	Adult starting dosage range (mg/day)	Adult maintenance dosage range (mg/day)	Therapeutic plasma levels (ng/mL)	Cytochrome P450 isozymes affected/ Other features
Tricyclic antidepressants (TCAs) (generics available for all listed below) *(continued)*					
Imipramine (Tofranil)	C: 75, 100, 125, 150 mg T: 10, 25, 50 mg	75–100	150–300	150–250[b]	
Maprotiline (Ludiomil)	T: 25, 50, 75 mg	25–75	100–225		
Nortriptyline (Pamelor)	C: 10, 25, 50, 75 mg T: 25 mg LC: 10 mg/5 mL	10–25	75–150	50–150	Most noradrenergic of TCAs
Protriptyline (Vivactil)	T: 5, 10 mg	5–15	15–60	70–250	
Trimipramine (Surmontil)	C: 25, 50, 100 mg	25–75	150–300		
Monoamine oxidase inhibitors (MAOIs)					
Isocarboxazid (Marplan)	T: 10 mg	20	30–60		
Phenelzine (Nardil)	T: 15 mg (generic available)	45	15–90		
Selegiline (Eldepryl, Zelapar, EmSam)	C: 5 mg T: 5 mg T (disintegrating): 1.25 mg Transdermal patch: 6, 9, 12 mg/24 hours (generic of C/T available)	C/T: 5–10 Transdermal patch: 6	C/T: 30–60 Transdermal patch: 6–12		
Tranylcypromine (Par					

TABLE 14–1. Currently available medications for the treatment of major depressive disorder in the United States *(continued)*

Medication	Preparations/ dosages	Adult starting dosage range (mg/day)	Adult maintenance dosage range (mg/day)	Therapeutic plasma levels (ng/mL)	Cytochrome P450 isozymes affected/ Other features
Norepinephrine-dopamine reuptake inhibitors (NDRIs)					
Bupropion (Wellbutrin, Zyban, Budeprion, Buproban, Aplenzin, Forfivo)	T: 75, 100 mg SR (Zyban, Budeprion, Buproban): 100, 150, 200 mg XR (Aplenzin): 174, 348, 522 mg XL: 150, 300, 450 mg (generic available for most preparations, but generic Budeprion XL recalled)	T: 75–100 XR (Aplenzin): 174 SR: 150 XL: 150	T: 300–450 XR (Aplenzin): 348–522 SR: 300–400 XL: 300–450		Inhibitor—2D6 Use caution when prescribing in eating disorders
Mixed serotonin receptor agonists/antagonists (SRAs)					
Trazodone (Oleptro, Desyrel)	T: 50, 100, 150, 300 mg XR (Oleptro): 150, 300 mg (generic available except Oleptro)	T: 150 XR: 150	T: 200–600 XL: 150–375		Major risk of priapism
Nefazodone (Serzone)	T: 50, 100, 150, 200, 250 mg (generic available)	200	400–600		Inhibitor—3A4 Major risk of hepatotoxicity
Vilazodone (Viibryd)					

TABLE 14–1. Currently available medications for the treatment of major depressive disorder in the United States *(continued)*

Medication	Preparations/ dosages	Adult starting dosage range (mg/day)	Adult maintenance dosage range (mg/day)	Therapeutic plasma levels (ng/mL)	Cytochrome P450 isozymes affected/ Other features
α_2-Adrenergic receptor antagonists					
Mirtazapine (Remeron/ Soltab)	T: 7.5, 15, 30, 45 mg T (disintegrating): 15, 30, 45 mg (generic available)	15	15–60		May have synergistic antidepressant effects with SNRIs

Note. T=tablet; C=capsule; LC=liquid concentrate or solution; DR=delayed release; CR=controlled release; SR=sustained release; XR/XL=extended release

[a]Levels of amitriptyline+nortriptyline.

[b]Levels of imipramine+desipramine.

and tofu. Therefore, patients must be forewarned about dietary restrictions and the early warning signs of hypertensive crisis such as severe headache, palpitations, chest pain, or diaphoresis. Patients treated with MAOIs should be given clear instructions to present to the nearest emergency room for prompt treatment if they have symptoms consistent with a hypertensive reaction, including a pounding headache and flushing. Additionally, some practitioners provide patients with a short-acting antihypertensive (e.g., nifedipine or nitroglycerin) for prehospital care; however, this has not been conclusively demonstrated to decrease the incidence of myocardial infarction, stroke, and other end-organ damage as a result of hypertensive crises. Also, patients who are not experiencing a hypertensive crisis may take these medications, leading to hypotension. Finally, MAOIs should not be prescribed concomitantly with serotonergic antidepressants and other medications with serotonergic activity (e.g., opioids, triptans, psychostimulants, illicit drugs, tryptophan, some herbal medications) to reduce the risk of serotonin syndrome, a potentially lethal disorder characterized by delirium, tachycardia, hypertension, myoclonus, and hyperreflexia (see Table 14–1 for a listing and brief review of frequently prescribed antidepressant MAOIs in the United States).

Second-Generation Antidepressants

Selective Serotonin Reuptake Inhibitors

Since the release of fluoxetine in the United States in December 1987, SSRIs have advanced the pharmacological treatment of MDD. SSRIs with an FDA-approved indication for MDD are fluoxetine, sertraline, paroxetine, citalopram, and escitalopram. (Fluvoxamine does not have an MDD indication, although it is often prescribed for mixed depression and anxiety disorders like obsessive-compulsive disorder.) These medications do not appear to be more efficacious than the older antidepressants, and their superiority to placebo in milder depression has been questioned (Fournier et al. 2010). SSRIs have clear value in more severely ill patients to alleviate symptoms and decrease the risk of suicide. The real advantage of these medications over their predecessors is the more benign side effect profile and minimal risk of lethality with intentional overdose. This has led to a remarkable increase in prescriptions for antidepressants by primary care physicians (Pirraglia et al. 2003).

Adverse effects are typically neuropsychiatric (headache, dizziness, fatigue, insomnia), gastrointestinal (nausea, constipation, diarrhea), excessive sweating, and sexual dysfunction for both men and women (decreased libido, impaired arousal, delayed orgasm and/or anorgasmia). Even though many SSRIs are approved for the long-term treatment of anxiety disorders, SSRI-induced anxiety and agitation are very common during treatment initiation or dose titration. As a result, many practitioners will start the medication at a low dose and titrate slowly, especially in anxious or highly somatic patients. Prescribers may also give a short course of an as-needed benzodiazepine during initiation and dose titration for acute anxiolysis. There is a transient increased risk of suicidal thinking in adolescents and young adults (leading to the FDA's "black box" warning) after drug initiation and during dose titration. Psychiatric prescribers should be alert for increased activation or suicidal

ideation as the anergia and other neurovegetative symptoms of depression may abate in advance of improved mood. With the exception of paroxetine, all SSRIs have minimal anticholinergic, antihistaminic, and anti-α-adrenergic side effects. Unlike the TCAs, they do not cause cardiac conduction delay, and owing to their lack of effects on norepinephrine reuptake, tachycardia is rare; this benign cardiac profile substantially limits their toxicity in overdose.

Several of the SSRIs, including paroxetine, fluoxetine, and, to a lesser extent, sertraline and fluvoxamine, inhibit the drug-metabolizing enzyme cytochrome P450 (CYP) 2D6 (Nemeroff et al. 1996). Commonly used medications that are metabolized by CYP2D6 include most antidepressants and antipsychotics, some beta-blockers, and codeine. Fluvoxamine, fluoxetine, and sertraline also inhibit CYP3A4. This inhibition may increase the plasma levels of some benzodiazepines, carbamazepine, cyclosporine, erythromycin, quinidine, and lidocaine. Fortunately, even though these drugs are often co-prescribed, serious adverse events are rare.

Serotonin reuptake inhibitors, including TCAs with serotonergic properties and SNRIs (discussed in a later subsection), may cause adverse symptoms on abrupt discontinuation or even with dose reduction (Shelton 2006). These symptoms include anxiety, flu-like symptoms, myoclonus, paresthesia, and transient electric shock sensations in the extremities (Shelton 2006). Such adverse symptoms are a greater problem with medications with shorter half-lives such as paroxetine or the SNRIs venlafaxine and desvenlafaxine and can be reduced by a slow or slower tapering or the substitution of a longer half-life serotonergic antidepressant such as fluoxetine. Patients using these medications should be warned about these effects in advance of prescribing (see Table 14–1 for a listing and brief discussion of frequently prescribed SSRIs in the United States).

Norepinephrine-Dopamine Reuptake Inhibitors

Bupropion is the only FDA-approved antidepressant that selectively increases synaptic dopamine and norepinephrine without affecting serotonin (although some tricyclics, such as desipramine, predominantly act on the latter). Bupropion is a very weak norepinephrine and dopamine reuptake inhibitor; its principal mechanism of action is the stimulation of presynaptic release of norepinephrine, dopamine, and possibly norepinephrine (Ghanbari et al. 2011). Bupropion also appears to be as efficacious as any other first- or second-generation antidepressant. However, it may be better tolerated than other antidepressants, especially relative to the first- and some second-generation medications (e.g., SSRIs and SNRIs induced-sexual dysfunction). The medication also has minimal effects on anxiety symptoms (Tomarken et al. 2004) and should not be used as a primary antidepressant in patients with comorbid anxiety disorders.

Bupropion has a side-effect profile that distinguishes it from other newer antidepressants (i.e., increased agitation/anxiety, decreased appetite, weight loss, and insomnia compared with some of the more typical neurological and gastrointestinal side effects). The major limiting side effects, albeit rare, are seizures and mild hypertensive reactions. These serious side effects are dose-related, and the maximum bupropion dosage should be capped at 450 mg/day. The risk of seizures also increases in patients with eating disorders and binge-purging behaviors, so bupropion usually should not be

prescribed to patients with eating disorders even though they may request these medications because of its weight loss properties (see Table 14–1 for a review of buproprion preparations and dosing in the United States).

Serotonin-Norepinephrine Reuptake Inhibitors

There are four "modern" SNRIs with FDA approval for the treatment of MDD in the United States: venlafaxine; its major active metabolite, desvenlafaxine; duloxetine; and levomilnacipran, the active enantiomer of racemic milnacipran. Like the older TCAs, these medications inhibit the reuptake of serotonin and norepinephrine and have a similar but attenuated side-effect burden. These medications are also as effective as the older antidepressants but for some patients may be less well tolerated than other newer antidepressants like SSRIs because of their side effects. In addition, venlafaxine and desvenlafaxine are known to produce severe discontinuation symptoms. Venlafaxine and desvenlafaxine cause sympathomimetic side effects (hypertension, tachycardia, diaphoresis), especially at higher dosages, where these medications have stronger noradrenergic properties.

Venlafaxine and desvenlafaxine are also prone to discontinuation reactions as noted earlier. Venlafaxine and duloxetine both have been FDA-approved for the treatment of generalized anxiety disorder. Duloxetine also has efficacy in the treatment of chronic pain syndromes and is approved for the management of fibromyalgia, diabetic neuropathy, and chronic musculoskeletal pain disorders like osteoarthritis. Notably, the approved dosage range for depression is 30–60 mg/day, but for pain the recommended dosage ranges up to 120 mg/day. Levomilnacipran was approved in July 2013 for the treatment of major depressive disorder (racemic milnacipran is currently only FDA-approved for the treatment of fibromyalgia). Levomilnacipran has the benefit of once-daily dosing with theoretically more noradrenergic dosing than other members of the class (Saraceni et al. 2013).

The SNRIs have also been used in combination with other newer antidepressants; for example, venlafaxine plus mirtazapine is an effective combination strategy, which is discussed in greater detail later in this chapter (see Table 14–1 for a listing and brief discussion of available SNRI preparations and dosing in the United States).

Mixed Serotonin Agonists/Antagonists

There are several mixed serotonin agonists/antagonists on the market. Nefazodone and trazodone weakly inhibit serotonin reuptake and are 5-HT_{2A} and 5-HT_{2C} (postsynaptic) serotonin receptor antagonists. Approved by the FDA in January 2011, vilazodone is also an SSRI, but unlike its classmates, it has unique $5HT_{1A}$ partial agonist properties (similar to those of the anxiolytic buspirone). The most recently FDA-approved antidepressant for the treatment of MDD is vortioxetine, which has a mechanism of action similar to that of vilazodone, with both serotonin reuptake inhibitor and a complex agonist/antagonist effects (including partial profile at multiple serotonin receptors). Although not presently available in the United States, agomelatine is a 5-HT_{2C} serotonin receptor antagonist with agonist effects at melatonin MT_1 and MT_2 receptors, which may render it a more effective soporific in depression with prominent insomnia. Agomelatine has been shown to correct circadian misalignment, particularly phase-delayed

sleep (falling asleep and waking later). In fact, correction of circadian rhythm disturbance, along with improved sleep quality and architecture, may be responsible for some of its antidepressant effects (Carney and Shelton 2011).

Nefazodone is associated with less anti-α_1-adrenergic and anticholinergic side effects than trazodone; therefore, there is less risk of orthostatic hypotension, sedation, and confusion with the former. Additionally, nefazodone is a potent inhibitor of CYP3A4 and, when combined with SSRIs, has been reported to cause serotonin syndrome (John et al. 1997; Smith and Wenegrat 2000), with another case report of serotonin syndrome with low-dose trazodone added to nefazodone (Margolese and Chouinard 2000). Nefazodone is associated with a lower incidence of sexual dysfunction (Serretti and Chiesa 2009), and this popularized its treatment among depressed patients who were especially concerned about sexual side effects with SSRIs. Unfortunately, nefazodone can, albeit rarely, cause early onset and severe hepatotoxicity, including liver failure, which has limited its clinical use (Stewart 2002). Because of its powerful anti-α_1-adrenergic and anticholinergic properties, trazodone causes orthostatic hypotension and sedation, which can result in falls in the elderly. The sedative side effects have popularized its off-label use as a hypnotic in low doses, although there is minimal efficacy evidence over placebo in insomnia beyond the first few weeks of treatment. A rare but potentially severe side effect of both nefazodone and trazodone is priapism, a medical emergency requiring rapid surgical intervention. Finally, because of its ability to block potassium channels, trazodone has been associated with cardiac arrhythmias and, in conjunction with its anti-α_1-adrenergic effects, should be prescribed with extreme caution to patients with underlying cardiovascular and cardiac conduction disease.

Vilazodone's side-effect profile is similar to those of the SSRIs. A more complete side-effect profile outside of the clinical research setting is likely to emerge from phase IV (postmarketing) monitoring. Vilazodone should be taken with food to maximize absorption. Finally, vilazodone is inhibited by CYP3A4, so lower doses are recommended when vilazodone is co-administered with potent CYP3A4 inhibitors like antifungal agents.

Finally, vortioxetine has demonstrated efficacy over placebo in some but not all, and over placebo and active SNRI comparators in several short-term (6- to 8-week), randomized, double-blind, placebo-controlled trials (including one in older adults) (Alvarez et al. 2011; Baldwin et al. 2012; Boulenger et al. 2013; Henningsberg et al. 2012; Jain et al. 2013; Katona et al. 2012; Mahableshwarkar et al. 2013). Vortioxetine has also been reported to be an effective maintenance strategy for relapse prevention in MDD (Alam et al. 2014; Boulenger et al. 2012). Vortioxetine has been well tolerated in these studies, with a side-effect profile typical of a serotonergic antidepressant (e.g., gastrointestinal distress and mild neurological symptoms). Most metabolism is hepatic via CYP2D6, so precautions must be taken when vortioxetine is co-administered with CYP2D6 modulators (see Table 14-1 for a discussion of mixed serotonin agonists/antagonists prescribing practices in the United States).

Alpha$_2$-Adrenergic Receptor Antagonists

The only medication in this class approved for the treatment of MDD in the United States is mirtazapine (the similarly acting mianserin is approved in Europe).

Mirtazapine's presynaptic α_2-adrenergic receptor antagonist effects increase norepinephrine release. Mirtazapine is also a potent 5-HT_{2A}, 5-HT_{2C}, and, to a lesser extent, 5-HT_3 receptor antagonist. This combination of pharmacological properties increases synaptic monoamine levels. In addition, mirtazapine has potent antihistaminergic effects that can cause weight gain and/or excessive sedation. Because of the latter, mirtazapine is often prescribed at bedtime as a first-line agent in treating MDD with significant insomnia.

Mirtazapine has little potential for clinically significant drug-drug interactions because of minimal effects on CYP isoenzymes; therefore, it is often prescribed in the depressed medically ill and geriatric depression. The combination of serotonin antagonist properties may be associated with the lower risk for gastrointestinal side effects and sexual dysfunction relative to other newer antidepressants.

Finally, as discussed earlier, mirtazapine has been effectively combined with the SNRI venlafaxine in large multi-site real-world effectiveness trials for TRD and may be a safe and effective combination agent with SSRIs, even at treatment initiation (Blier et al. 2009) (see Table 14–1 for a review of mirtazapine preparations and dosing in the United States).

Combination and Adjunctive Antidepressant Strategies in Treatment-Resistant Unipolar Depression

In the 1990s, the National Institute of Mental Health (NIMH) funded the largest prospective real-world multi-site effectiveness trial in MDD, Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (Gaynes et al. 2008, 2009). Briefly, STAR*D was an "all-comers" effectiveness trial with relatively liberal recruitment that enrolled about 4,000 unipolar depressed outpatients. All subjects began the study by receiving citalopram for 6 weeks; at the end of this first and each subsequent phase, subjects were assessed for response and remission of their depressive symptoms. Only about one-third of the subjects experienced remission in the initial phase. The remaining approximately two-thirds were regarded as having "treatment resistant" depression and invited to enter a selective randomization design. These subjects first indicated if they were interested in receiving evidence-based psychotherapy (cognitive therapy) or continuing with medications. If they decided on the latter, subjects were randomly assigned to receive adjunctive cognitive therapy and switched in-class to sertraline or out-of-class to venlafaxine or bupropion. Subjects could also be randomly assigned to augmentation with either buspirone or bupropion. If subjects were randomly assigned to one of the cognitive therapy arms, did not experience remission, and remained interested in continuing in the protocol, they were then randomly assigned to receive either bupropion or venlafaxine. At the next level (level 3), subjects whose depression did not remit were switched to either mirtazapine or nortriptyline, or their current antidepressant was augmented with either lithium or triiodothyronine. At step 4, all medications were stopped, and those subjects wishing to continue were randomly assigned to receive either tranylcypromine or the combination of venlafaxine and mirtazapine. Finally, subjects whose depression did not remit at step 4 were offered a course of electroconvulsive ther-

apy (ECT) outside of the protocol. As anticipated, the rates of response and remission decreased with each subsequent failed trial; perhaps less expected though was the lack of an efficacy difference with *any* of the interventions (including monotherapy and augmentation with cognitive therapy).

Another real-world effectiveness trial, Combining Medications to Enhance Depression Outcomes (CO-MED), compared SSRI antidepressant monotherapy and combined antidepressant treatment (Rush et al. 2011). In this study, 665 moderately depressed nonpsychotic outpatients were enrolled at 15 primary care or psychiatric clinics and randomly assigned (in single-blind fashion) to receive escalating doses of either escitalopram (up to 20 mg/day) and placebo, escitalopram (up to 20mg/day) and bupropion (up to 400 mg/day), and extended-release venlafaxine (up to 300 mg/day) and mirtazapine (up to 45 mg/day). All retainers were followed for two phases: acute phase of 12 weeks and extended follow-up of 7 months. Again, there was no statistically significant difference in response and remission rates among the three different treatment arms (albeit venlafaxine and mirtazapine were associated with a great side-effect burden). On secondary analysis, the following phenotypic correlates also did not predict a better response to SSRI monotherapy versus the combination arms: race/ethnicity (Lesser et al. 2011), comorbid general medical conditions (Morris et al. 2012), baseline depression severity (Friedman et al. 2012), depression chronicity (Sung et al. 2012) and depressive subtypes (melancholic [Sung et al. 2012] and anxious [Chan et al. 2012] subtypes).

These disheartening real-world results in TRD have motivated the investigation of novel antidepressant (including nonpharmacological) treatment options, which has resulted in several alternative treatment strategies including lead compounds with antidepressant effects that are more rapid and robust than those of monoaminergic antidepressants. We will review some of these novel pharmacological interventions later. First, we discuss novel evidence-based approaches not studied in STAR*D and CO-MED. (See Shelton et al. 2010 for a more complete review of evidence-based adjunctive/augmenting strategies in TRD.)

Second-Generation Antipsychotics

Although they have not been compared head-to-head with other augmentation strategies in effectiveness trials, several second-generation antipsychotic (SGA) medications have large effect sizes for augmentation in unipolar depression, as revealed by Nelson and Papakostas (2009) in their landmark meta-analysis. All available data for the SGAs olanzapine, risperidone, quetiapine, and aripiprazole were probed. (At the time of writing, there were no available trials with the other available SGAs, ziprasidone, paliperidone, lurasidone, asenapine, or iloperidone.) The overall response odds ratio (OR) for SGA versus placebo was 1.69 (95% CI=1.46–1.95, $z=7.00$, $N=16$, $P<0.00001$). ORs grouped by atypical agent were variable, from 1.39 (95% CI=1.05–1.84) to 2.07 (95% CI=1.58–2.72). The remission OR was 2.00 (95% CI=1.69–2.37, $z=8.03$, $N=16$, $P<0.00001$). The ORs for remission varied from 1.83 to 2.63 among the drug subgroups, with similarly overlapping confidence intervals. The pooled remission rate was 30.7% for SGA vs. 17.2% for placebo, with a calculated number needed to treat (NNT) of 9. Albeit effective, discontinuation rates attributed to adverse medication effects were higher with SGAs (9.1%)

versus placebo (2.3%), with a calculated number needed to harm of 17.

Although the SGAs are more effective than other accepted augmentation strategies like lithium and thyroid hormone augmentation, the increased risk of side effects (including metabolic syndrome and extrapyramidal side effects) requires a strong therapeutic alliance as well as careful and consistent weight, vital sign, and neurological and laboratory monitoring. Most SGAs remain proprietary and may be prohibitively expensive for patients without entitlements (augmentation with the less-expensive first-generation antipsychotics has not been formally tested in randomized controlled trials).

Nutraceuticals

The interest in complementary and alternative medicine (CAM) in the past several decades has influenced all areas of allopathic medicine, including psychiatry. Although the initial hope of some CAM treatments did not live up to expectations (e.g., St. John's wort, echinacea), other nutraceuticals (e.g., omega-3 fatty acids, folic acid/L-methylfolate, S-adenosylmethionine [SAMe]) have emerged as more accepted augmenting strategies in TRD.

Omega-3 Fatty Acids

There is mixed efficacy data for omega-3 fatty acid monotherapy or adjunctive supplementation in both unipolar (Bloch and Hannestad 2012) and bipolar (Sarris et al. 2012) depression. A recent meta-analysis had lack of efficacy data for MDD trials due to publication bias—namely, poor methodological quality and lack of intention-to-treat analyses (Bloch and Hannestad 2012). All omega-3 fatty acids have a double bond in position 3 of their carbon chain. In the Western diet, the most frequently ingested omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-6 fatty acids or their precursors are more abundant in the Western diet than omega-3 fatty acids or their precursors—linoleic acid, alpha-linoleic acid, and arachidonic acid. An elevated omega 6–to–omega 3 ratio alters plasma membrane fluidity and increases levels of proinflammatory mediators like arachidonic acid, an omega-6 fatty acid found in cell membranes and a metabolic precursor of the inflammatory eicosanoids (prostaglandins and thromboxanes). Prior studies in MDD have used relatively high doses of both EPA and DHA (several grams per day), and in some patients, the higher doses increased gastrointestinal symptoms like flatulence, diarrhea, and steatorrhea, which may have affected blinding. Because of the relatively benign side-effect profile, omega-3 fatty acids are, at the very least, a safe augmenting trial for some patients with TRD who are interested in CAM strategies.

Folic Acid/L-Methylfolate

Folic acid is a critical component of the one-carbon cycle that results in nucleic acid synthesis. Low folate levels have been associated with depression (Gilbody et al. 2007). A 2004 meta-analysis demonstrated a small but measurable effect for folic acid as an adjunct in MDD, although it is unclear if folic acid or its derivatives are useful in the treatment of depressed nondeficient patients as monotherapy (Gilbody et al. 2007). Most positive augmentation studies with folic acid supplementation occurred prior to 1998, when the FDA (and many other regulatory agencies) began requiring folic acid fortification of foods (Smith 2007). Folate deficiency is now rare in the U.S. population because foods are now fortified with

folic acid. The small response of folic acid in prior studies may have been observed predominantly in deficient depressed patients.

Folic acid is metabolized in several steps to its active form, L-methylfolate. L-methylfolate is a co-factor in the synthesis of tetrahydrobiopterin (BH4) and other important physiological functions. BH4 is a co-factor for both tyrosine and tryptophan hydroxylases; therefore, it is important in the synthesis of the three key monoamine neurotransmitters affected by antidepressants: dopamine, norepinephrine, and serotonin (Stahl 2007). There are polymorphic variants of several enzymes related to L-methylfolate synthesis and function. L-Methylfolate is approved by the FDA as a medical food product; it is marketed as adjunct in TRD, although the FDA has not officially approved that indication. As an augmentation strategy, L-methylfolate at 15 mg/day, but not at 7.5 mg/day, demonstrated clinical benefit in SSRI-resistant MDD (Papakostas et al. 2012). Although the cost may be prohibitive for some patients, like most other nutraceuticals, L-methylfolate is generally well tolerated with minimal adverse effects (Fava et al. 2011).

S-Adenosylmethionine

SAMe was first made commercially available in the 1970s and was subsequently released in the United States in an enteric-coated formulation as an over-the-counter dietary supplement. Like folic acid, SAMe is a critical mediator in the one-carbon cycle as a major methyl donor in the synthesis of amino acid neurotransmitters and other neuromodulators. There have been several trials of SAMe antidepressant monotherapy with equivocal results compared with placebo and an active TCA comparator. However, a recent randomized, placebo-controlled, double-blind trial in antidepressant nonresponders suggested that adjunctive SAMe is safe, well tolerated, and effective (NNT response=6, NNT remission=7) (Papakostas et al. 2010). SAMe also improves memory deficits in MDD (Levkovitz et al. 2012) and alters serum levels of anticipated pathway intermediaries like the proinflammatory homocysteine (Mischoulon et al. 2012).

Somatic and Neuromodulatory Therapies

Electroconvulsive Therapy

In refractory depressive disorders, ECT remains the gold standard of treatment. Unfortunately, it is often not considered *early enough* in the treatment algorithms of most psychiatry practitioners. ECT should be considered as a first-line option for major depression with catatonic features, psychotic depression, postpartum depression/psychosis, and when depression is life threatening (e.g., very active suicidal intention or in the face of limited oral intake) (for further discussion of ECT, see Chapter 15, "Brain Stimulation Treatments for Mood Disorders").

Light Therapy

Bright light therapy (also known as phototherapy) is a well-established treatment for seasonal affective disorder (Blazer et al. 1998; McClung 2007). Although it has been extensively studied as monotherapy, there is also evidence that bright light therapy may be useful as an adjunct in nonseasonal depression (Even et al. 2008). Light therapy is non-invasive and is a relatively inexpensive alternative to

other neuromodulatory therapies and has few adverse effects. The major concerns are emergent hypomania and autonomic activation, which the psychiatric clinician should monitor, especially early in the course of treatment. The light of standard incandescent or florescent bulbs is not sufficient, and a specially made light box is typically required. The light requirements for effective phototherapy is exposure to 10,000 lux (lumens per square meter) for at least 30 minutes. If problem side effects occur, the time may need to be reduced, with a slow advance to the full 30 minutes. Longer light exposures may be needed for some patients.

Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) is rising in popularity as a treatment alternative for TRD that is FDA-approved in patients who have failed one but no more than two standard antidepressant trials (see Chapter 15). In practice, however, rTMS is typically used further down the treatment algorithm. rTMS is non-invasive (no need for general anesthesia, neuromuscular blockade, or seizure induction as with ECT) and is generally well tolerated. A typical course is 15-minute sessions about four or five times per week for several weeks before efficacy is assessed. The rTMS coil applies fast stimulation rates (>5 Hz) to the scalp in order to stimulate the hypofunctional prefrontal cortex in unipolar depression. Common side effects in active versus sham treatment include headache at the site of stimulation, jaw pain/claudication, and facial muscle twitching. The main limiting factor in rTMS is cost-related because of the potential lack of third-party insurance reimbursement when used outside of FDA indications.

Vagal Nerve Stimulation

Vagal nerve stimulation (VNS) is further down the treatment algorithm than the aforementioned neuromodulatory therapies. It consists of neurosurgical implantation of a stimulating electrode around the left vagus nerve adjacent to the carotid artery, which provides intermittent depolarizing electrical currents. The antidepressant mechanism of action for VNS has been an area of active preclinical and clinical investigation (see Chapter 15).

Deep Brain Stimulation

Patients with the most treatment-refractory depression may be referred for deep brain stimulation. There are very few sites in the United States with the neurosurgical expertise to reliably and safely implant indwelling electrodes (see Chapter 15).

Novel Experimental Treatments

Glutamate-Based Medications

Because of the current market surfeit of monoaminergic antidepressants and the lack of global response in STAR*D, novel treatment options based on alternative mechanisms of action have occupied the attention of many depression research groups in the past 20 years. Several medications with glutamatergic mechanisms of action were fortuitously discovered, and as with the SSRIs, this has spurned interest from the pharmaceutical industry to develop more specific compounds with fewer untoward effects. In 2000, Berman et al. reported the first randomized, placebo-controlled cross-over design trial ($N=7$) of a single subanesthetic

infusion of 0.5 mg/kg ketamine, a *N*-methyl-D-aspartate (NMDA) receptor antagonist and FDA-approved anesthetic agent, in major depression. In this study, ketamine had rapid and robust antidepressant effects within hours that lasted for up to 1 week (Berman et al. 2000). Since that initial report, there have been two other randomized, placebo-controlled trials (Valentine et al. 2011; Zarate et al. 2006) and numerous open-label studies with both single (Ibrahim et al. 2012a; Mathew et al. 2010; Phelps et al. 2009; Price et al. 2009) and repeated (aan het Rot et al. 2010; Messer et al. 2010; Murrough et al. 2012) infusion paradigms of subanesthetic-dose ketamine. Unfortunately, because of its transient psychotomimetic effects even at these low doses, the potential for abuse and the uncertainty about long-term sequelae (there have been reports of vacuolar neuropathological changes in postmortem series from chronic ketamine abusers) have motivated development of novel antidepressant medications with glutamatergic effects. CP-101,606, an intravenous NR2B subtype–specific NMDA receptor antagonist, demonstrated preliminary antidepressant efficacy without reported dissociative side effects in an industry-sponsored randomized controlled trial (Preskorn et al. 2008). In a preclinical report, another NR2B-specific NMDA receptor antagonist, Ro-25-6981, decreased anhedonic-like (impaired sucrose preference) behavior in rodents exposed to chronic unpredictable stress (Li et al. 2011). A small study by our group demonstrated the efficacy of orally administered MK-0657, a NR2B-specific antagonist, in TRD (Ibrahim et al. 2012b). More recently, we completed a randomized, double-blind, placebo-controlled pilot study evaluating the potential rapid antidepressant efficacy and tolerability of a single intravenous formulation of the low-trapping NMDA antagonist AZD6765 (150 mg) in 22 patients with TRD-MDD. Within 80 minutes, Montgomery-Åsberg Depression Rating Scale scores improved in subjects receiving AZD6765 compared with placebo (d = .40); however, this improvement was short-lived (Zarate et al. 2013). The antidepressant efficacy of AZD6765 in TRD-MDD was independently demonstrated in a subsequent study (Sanacora et al. 2013).

Other medications with non-NMDA glutamatergic activity have demonstrated preclinical and clinical antidepressant effectts. Riluzole currently has an FDA-approved indication for delaying disease progression in amyotrophic lateral sclerosis (ALS). It has also been demonstrated to have antidepressant efficacy in an open-label monotherapy trial (Zarate et al. 2004) and as an adjunct in treatment-refractory unipolar depression (Sanacora et al. 2004, 2007). Although its mechanism of action is not fully understood as an antidepressant, riluzole exerts its effects on synaptic glutamate by at least two mechanisms: 1) inhibiting presynaptic voltage-gated sodium channels, which reduces vesicular glutamate release; and 2) increasing expression of the astrocytic glutamate reuptake transporter GLT1/EAAT2, which removes excessive glutamate from the synaptic cleft. Riluzole has also been investigated to augment and/or maintain response after a single subanesthetic infusion of ketamine. In two independent studies, riluzole augmentation did not improve response over oral placebo in the month following ketamine infusion (Ibrahim et al. 2012a; Mathew et al. 2010). In the Mt. Sinai study, riluzole appeared to delay time to subsequent relapse (which was close to significance in our group's report as well, based on survival analysis) (Ibrahim et al. 2012a).

Metabotropic glutamate receptor 2/3 (mGluR2/3) antagonists improve resiliency in the rodent forced swim test (FST), with concomitant neurochemical changes consistent with those of other glutamatergic antidepressants like ketamine (increased postsynaptic density protein of 95 kilodaltons [PSD-95] expression and mammalian target of rapamycin [mTOR] activation) (Belozertseva et al. 2007; Dwyer et al. 2012; Liu et al. 2012). Several metabotropic glutamate receptor 5 (mGluR5) antagonists and negative allosteric modulators have antidepressant efficacy in rodent models of despair (Tatarczynska et al. 2001). However, as detected by positron emission tomography and immunohistochemistry in postmortem brain tissue, mGluR5 levels are *decreased* in MDD (Liu et al. 2012). Although this finding appears inconsistent with the reported efficacy of mGluR5 antagonists in preclinical reports, this downregulation in humans may be compensatory. Hoffmann-La Roche recently completed a phase II trial of the mGluR5 negative allosteric modulator (antagonist) RO4917523 as monotherapy in TRD; at the time of writing, these results have yet to be released to the public. However, they have begun recruitment for a larger phase II randomized, double-blind, placebo-controlled trial of RO4917523 for TRD augmentation (ClinicalTrials.gov identifier: NCT01437657).

Glycine transporter inhibition is another novel treatment strategy in major depression because of its indirect efficacy on glutamatergic neurotransmission by inhibiting glycine (co-agonist with glutamate) transport. The Naurex, Inc. compound GLYX-13, a glycine transporter type 1 receptor (GlyT1) inhibitor, has been studied in a four-arm, single intravenous infusion (1 mg/kg, 5 mg/kg, 10 mg/kg, and placebo) protocol. Naurex has also begun recruitment with GLYX-13 for augmentation in the treatment of TRD (ClinicalTrials.gov identifier: NCT01684163).

Other Experimental Therapies

Other novel approaches have provisional efficacy for unipolar depression. First, low-field magnetic stimulation (LFMS) is a non-invasive experimental therapeutic option based on the clinical report of rapid symptom relief in bipolar depression after exposure to a magnetic field such as that generated by MRI (Rohan et al. 2004). Larger, multi-site, sham-controlled studies are needed to confirm the efficacy of LFMS as a rapidly acting antidepressant in unipolar depression.

Some anticholinergic medications also have antidepressant effects. The $\alpha_4\beta_2$ nicotinic cholinergic receptor antagonist mecamylamine was a lead compound in both preclinical and clinical depression protocols (Philip et al. 2010). However, the Targacept compound TC-5214, an analogue of mecamylamine, did not separate from placebo as an adjunctive treatment in MDD in at least one of the four completed clinical trials (Ledford 2011). Like ketamine, the muscarinic cholinergic receptor antagonist scopolamine has demonstrated rapid antidepressant effects in MDD (Drevets and Furey 2010; Furey and Drevets 2006). Scopolamine's antidepressant and anxiolytic effects are more dramatic in females (Furey et al. 2010), and baseline self-reported mood on the Profile of Mood State (POMS) questionnaire was found to positively predict scopolamine's antidepressant response (85% predictive ability to prospectively discern responders from nonresponders) (Furey et al. 2012).

Several groups have investigated immunomodulatory therapy as treatment alternatives in MDD because of the ret-

rospective antidepressant effects of novel immunomodulators in autoimmune disease. For example, 618 subjects with moderate-to-severe psoriasis were randomly assigned to receive the tumor necrosis factor–alpha (TNF-α) monoclonal antibody etanercept or a placebo injection (Tyring et al. 2006). Although not the primary outcome of the study, etanercept resulted in about a 50% reduction in depression scores. Additionally, unlike fatigue, which appeared to be highly correlated with psoriatic symptomatology, relief of depression did not strongly correlate with improvement in the dermatological and/or musculoskeletal signs/symptoms of psoriasis. Although a recent placebo controlled trial of the TNF-α neutralizing antibody infliximab did not reveal global efficacy in TRD, subjects with a baseline level of the acute-phase reactant C-reactive protein (CRP) > 5 mg/L had a positive antidepressant response (Raison et al. 2013). Other novel immunomodulators (e.g., interleukin 1β and interferon inhibitors) are also rational drug targets awaiting development/design for MDD and other neuropsychiatric disorders with an immune component.

Finally, after the initial hope for but lackluster effects of corticotropin-releasing hormone (CRH) receptor antagonists in MDD trials, there is resurging interest in developing novel neuropeptidergic treatments. Some of the most promising translational targets are tachykinin receptors for substance P and other neurokinins. Several neurokinin-1 (NK1) receptor antagonists have been studied with equivocal results in phase II and III clinical trials. MK-869 (aprepitant), L559274, and CP122721 decreased depressive symptoms relative to placebo in phase II trials, and both MK-869 and CP122721 displayed fewer adverse side effects than active SSRI treatment (Kramer et al. 1998, 2004). MK-869 did not separate from placebo in a larger multi-site, placebo-controlled phase III study (with paroxetine as an effective active comparator) (Keller et al. 2006). A randomized controlled trial with another NK1 receptor antagonist, orvepitant (GW823296; GlaxoSmithKline) was terminated because of increased seizure risk. The NK3 receptor antagonist SR142801 (osanetant) also did not outperform placebo or the active comparator paroxetine (Holmes et al. 2003; Rupniak and Kramer 1999). Finally, the most promising neurokinin receptor antagonist to date for MDD, the NK2 receptor antagonist SR48968 (saredutant), relieved depression in both general adult and elderly depressed patients (Ebner et al. 2009). Several additional clinical trials with this compound are listed as completed on ClinicalTrials.gov, but the results have yet to be released.

DSM-5 and Depression

There have been several alterations to the diagnostic system in the newest iteration of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, DSM-5 (American Psychiatric Association 2013). The major alteration is the blurring of the diagnostic boundary between MDD and bereavement:

> In DSM-IV, there was an exclusion criterion for a major depressive episode that was applied to depressive symptoms lasting less than 2 months following the death of a loved one (i.e., the bereavement exclusion). This exclusion is omitted in DSM-5 for several reasons, including the recognition that bereavement is a severe psychosocial stressor that can precipitate a major depressive episode in a vulnerable individual, generally beginning soon after the loss, and can add an additional risk for suffering, feel-

> ings of worthlessness, suicidal ideation, poorer medical health, and worse interpersonal and work functioning. It was critical to remove the implication that bereavement typically lasts only 2 months, when both physicians and grief counselors recognize that the duration is more commonly 1–2 years. A detailed footnote has replaced the more simplistic DSM-IV exclusion to aid clinicians in making the critical distinction between the symptoms characteristic of bereavement and those of a major depressive disorder. (American Psychiatric Association 2013, p. 811)

Also, a mixed anxiety and depressive disorder was proposed to better capture the clinical phenomenology of the current anxious depression subtype. However, the DSM-5 Task Force determined that there was "insufficient evidence to warrant inclusion of" mixed anxiety and depressive disorder as a parsimonious clinical entity and left it out of DSM-5. A new specifier, "with anxious distress," was added. Otherwise, the MDD specifiers (e.g., severity, recurrence and the presence/absence of psychotic features) are unchanged in DSM-5. Special considerations continue for depressive subtypes as previously extrapolated from available research data (e.g., standard antidepressant + antipsychotic and lower threshold for ECT in psychotic depression and MAOI as second- or third-line treatment in refractory atypical depression).

Research Domain Criteria, Clinical Neuroscience, and Major Depressive Disorder

Although DSM-5 was recently published, an alternative research diagnostic strategy has been proposed that is not based on purely descriptive diagnostic categories. Instead, diagnoses will be made on the back of the rapid explosion of clinical neuroscience in neuropsychiatric disorders in the NIMH-sponsored and -advocated Research Domain Criteria (RDoC) (http://www.nimh.nih.gov/research-funding/rdoc/index.shtml). The RDoC project proposes a research-based domain "matrix" that spans the gamut of genes to behavior. Although certainly relevant to MDD, the RDoC project rejects traditional descriptive diagnoses to better evaluate neuroscientifically meaningful domains. These domains in MDD include negative valence (anhedonia, loss, frustrated reward) and cognitive matrices (attention, working memory, cognitive control). The RDoC work group notes that in the initial stages of the project, a sufficient research foundation will continue to be amassed to inform clinical diagnosis and treatment. As such, this system may not be an immediately useful paradigm shift for the psychiatric practitioner. Instead, RDoC's integrated neuroscientific framework from genomics to behavior may unpack heterogeneous categories that may remain forever inaccessible with purely descriptive diagnoses.

Another future direction in MDD treatment is the identification of clinically meaningful response biomarkers. Reliable biomarkers hold promise for future clinicians to increase the probability of treatment efficacy by complementing (or superseding) our present treatment selection strategies (e.g., past treatment response, positive family history of response, side-effect profile, patient preference, clinician preference, and, perhaps most commonly and least evidence-based, trial and error). As more antidepressants with novel mechanisms of action reach the market, it will be useful to

be able to stratify patients based on genetics, biochemistry, neurophysiology, or symptom features for predictive purposes—namely, depressed patients more likely to respond to a monoaminergic than to a glutamatergic antidepressant. As an example, a family history of alcohol dependence predicts a more rapid, robust, and sustained antidepressant response to ketamine in both unipolar (Phelps et al. 2009) and bipolar (Luckenbaugh et al. 2012) depression. Therefore, a family history of alcohol dependence is a potential genetic marker of antidepressant response to antiglutamatergic neuromodulators. Depressed patients with a strong genetic propensity to alcoholism may be more likely to respond than depressed patients without a family history of alcohol-related problems.

Conclusion

In this chapter, we have reviewed the pharmacological landscape and experimental horizon in MDD. Although it is in vogue to focus on their limitations, monoaminergic antidepressants remain the pharmacological mainstay in the treatment of unipolar depressive disorders, especially in treatment-naïve patients in whom the astute clinician has ruled out secondary causes of depression (e.g., hypothyroidism, vitamin deficiencies, infectious etiologies, medications and/or illicit substances). Although they were not the focus of this chapter, we are obliged to stress that evidence-based psychotherapies (e.g., cognitive-behavioral therapy, interpersonal therapy) are as effective first-line therapies in MDD treatment, especially with medication-wary and/or somatic patients and those with a strong personal preference for psychotherapy. The combination of antidepressant medication with evidence-based psychotherapies has synergistic benefits. Even in TRD, many evidence-based strategies exist (and we should often consider ECT *much earlier* in the treatment algorithm). On the other hand, as revealed by STAR*D, our current pharmacopeia is insufficient for many depressed patients, and some of the alternative targets include glutamatergic, anticholinergic, and neuropeptidergic medications. In addition to expanding available options, we also have an obligation to develop novel antidepressant medications with more rapid efficacy—namely, hours to days as opposed to weeks to a month, to better alleviate the burden of depression for patients, their families, and society at large.

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CHAPTER 15

Brain Stimulation Treatments for Mood Disorders

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Psychiatry is now developing a third realm of treatment modalities, complementing the well-established realms of psychopharmacology (medications) and psychotherapy. Different names are being proposed to describe these treatments, ranging from "neuromodulation" to "brain stimulation techniques" to the hard-to-understand and cumbersome term "nonpharmacological somatic treatments." As a class, these methods involve focal electrical brain stimulation of some sort, and they vary widely in their invasiveness and methods of delivery. Table 15–1 outlines most of the current methods.

In this chapter we review only those brain stimulation treatments that are U.S. Food and Drug Administration (FDA) approved to treat depressive disorders (electroconvulsive therapy [ECT], vagus nerve stimulation [VNS], transcranial magnetic stimulation [TMS]) or that have a large literature of human clinical trials in depressive disorders (deep brain stimulation [DBS], transcranial direct current stimulation [tDCS]). Brain stimulation methods are also being used in other psychiatric disorders (e.g., DBS and obsessive-compulsive disorder [OCD]) and in traditionally defined neurological disorders (e.g., DBS in dystonia or Parkinson's

TABLE 15–1. Overview of brain stimulation treatments

Acronym	Treatment	Convulsive?	Stimulation site	Psychiatric disorders	Clinical use status
ECT	Electroconvulsive therapy	Yes	Cortical	Depression, mania, catatonia	Grandfathered FDA approval
FEAST	Focal electrically administered seizure therapy	Yes	Cortical	Depression	Experimental, all conditions
MST	Magnetic seizure therapy	Yes	Cortical	Depression	Experimental, all conditions
rTMS	Repetitive transcranial magnetic stimulation		Cortical	Depression	FDA approval of two devices
VNS	Vagus nerve stimulation		Cervical cranial nerve	Depression	FDA approved for treatment-resistant depression
DBS	Deep brain stimulation		Subcortical	Depression	FDA approved for Parkinson's disease; HDE for OCD; pivotal trials in depression under way
tDCS	Transcranial direct current stimulation		Cortical	Substance abuse, depression	Experimental, all conditions
TENS	Transcutaneous electrical nerve stimulation		Peripheral nerve	Pain	FDA approved for pain conditions
EPI-fMRI	Echoplanar imaging–functional magnetic resonance imaging		Unknown—subcortical?	Depression	Experimental, all conditions
	Transcranial doppler ultrasound		Any	Unknown	Experimental, all conditions

Note. FDA = U.S. Food and Drug Administration; HDE = humanitarian device exemption; OCD = obsessive-compulsive disorder.

disease). We mention those uses in more traditional neurological disorders where appropriate, but a complete review of these areas is found in the references listed in "Recommended Readings" at the end of this chapter.

Finally, there are several brain stimulation techniques that are quite popular as research methods but that are unlikely to be used therapeutically in the near future. *Optogenetics* is a new method developed within the past 5 years in which individual cells are transfected with light-sensitive membrane ions and then stimulated with fiber optic light (LaLumiere 2011). This allows for exquisite spatial, temporal, and even histological specificity but requires gene vector transfection and an invasive light source implanted into the brain. To our knowledge this method has not been tried yet in humans. Similarly, there is much excitement about the potential for using *transcranial pulsed ultrasound*. For reasons that are not clear but that might involve mechanoreceptors sensitive to movement on neuronal cell membranes, pulsed ultrasound can cause certain neurons to discharge (conventional, nonpulsed ultrasound does not cause neuronal firing). The electrical discharge of neurons is not due to damage or heating. Pulsed ultrasound has been demonstrated in rabbits and rodents (http://www.youtube.com/watch?v=RGEP6iWLsvQ). An important question that will determine how popular this method becomes is whether one needs an open craniotomy to get the ultrasound past the skull. Ultrasound historically has had problems penetrating through bone and previously has not been performed in humans, except during brain surgery (Bystritsky et al. 2011). However, using phased arrays, Martin et al. employed high-intensity focused ultrasound noninvasively to induce medial thalatomies in patients with refractory chronic pain (Martin et al. 2009). Neuromodulatory ultrasound appears to be able to pass noninvasively through human cranium.

A fundamental concept for these techniques is that the brain is an electrochemical organ. All neurons transmit information and communicate with other cells through an electrical impulse (depolarization) traveling from a dendrite through the cell body out to the synapse. In our fascination with events happening chemically between neurons (psychopharmacology), with the exception of ECT, for years we have neglected or forgotten an important principle that the entire communication and action between neurons begins with an electrical impulse.

This renaissance in brain stimulation techniques would not be nearly as successful as it is without the revolution in brain imaging that has occurred over the past 20 years. Fundamentally, it is important to have hypotheses about where to stimulate. Thus, the results from brain imaging studies provide the needed knowledge base to hypothesize about where to apply the techniques. With some of the techniques, so-called functional brain imaging also allows one to guide the individual placement (as in, e.g., DBS). Although the regional neuroanatomy of the depressions is not as well defined as for example Parkinson's disease, we have a much better understanding of the regions involved in affective regulation, anxiety, or even hallucinations than we did 20 years ago. Brain stimulation techniques largely build on this body of knowledge from neuroimaging in guiding where in the brain they are applied. Once an area of the brain is targeted, the various brain stimulation technologies could potentially "turn on," turn off," or modulate that region. Although we call these "stimulation treatments," various characteristics (e.g., frequency, strength,

timing of stimulation) could actually lead to the treatment reducing unwanted activity (not stimulating or exciting).

Finally, it is rare to use any of the brain stimulation methods alone in treatment settings. Most commonly they are used in combination with medications or talking therapy. In fact, a most interesting area of research is to investigate how to combine the different stimulation techniques with medications or talking therapy. It seems likely that some medications, more than others, will work in synergy with a brain stimulation treatment for a particular disorder (Sackeim et al. 2009). Additionally, it is also likely that what a person is doing or thinking while being stimulated will ultimately matter in terms of clinical response (Vedeniapin et al. 2010). A particularly interesting line of research involves having patients actively crave a substance and then applying TMS to modify the emotional memory of the craving. Similarly, researchers are having patients with posttraumatic stress disorder remember their index trauma and are then applying TMS during the recall, or immediately after, again with the idea of modifying the ability to control the emotional response to the memory (Isserles et al. 2013). With the depressive disorders, this combination would likely involve pairing stimulation with either emoting or remembering sad events, or coupling the stimulation with forms of cognitive therapy designed to regain cognitive or cortical control of emotional reactions to situations or events.

Electroconvulsive Therapy

ECT is the oldest of the current brain stimulation treatments and involves the deliberate induction of a generalized tonic-clonic seizure by electrical means. Contemporary ECT devices typically deliver bidirectional (alternating current) brief-pulse square-wave stimulation through a pair of electrodes, which are applied externally to the patient's scalp. Given that the electricity must pass through the skin, bone, and scalp, a reasonable sized charge must be applied to have a therapeutic effect. ECT electrodes can be placed bifrontally, bitemporally (bilaterally), or unilaterally (often done to minimize cognitive effects). Because of the risk of bodily harm from the convulsion, ECT is performed under general anesthesia, with the body paralyzed. As with other convulsive therapies that historically preceded ECT, the goal is to produce a "controlled" seizure. The presence of seizure activity appears to be essential. Stimuli that are below the seizure threshold appear to be clinically ineffective. However, although the production of a seizure appears to be necessary, *a seizure alone is not sufficient.* Some forms of seizure induction are in fact clinically ineffective (Sackeim et al. 1993). In addition, there is some debate about the length of seizure needed to produce a clinical response (Lalla and Milroy 1996). Generally, the American Psychiatric Association Task Force on Electroconvulsive Therapy suggested a seizure of at least 20 seconds and definitely not longer than a few minutes (American Psychiatric Association 2001).

There are a variety of psychiatric and neurological conditions that respond favorably to ECT, although the majority of patients treated with ECT have a mood disorder, such as unipolar or bipolar depression, particularly when severe or accompanied by psychotic symptoms. Certain other conditions, such as mania,

schizoaffective disorder, catatonia, neuroleptic malignant syndrome, Parkinson's disease, and intractable seizures, may respond to ECT as well. Schizophrenia has also been treated with ECT, although the results tend to be less favorable and often transient as compared with those obtained in patients with mood disorders. Those patients with schizophrenia who also have a prominent disturbance of mood probably respond best to ECT.

For a typical series or a course of ECT, treatments are usually given two to three times per week for 8–12 treatments. Treatments can be conducted in either an outpatient or inpatient setting. This course may then be followed by maintenance treatment in the form of either medications, additional ECT given at less frequent intervals, or both.

A number of questions remain regarding the most effective methods for performing ECT, and its mechanism or mechanisms of action. The ECT team's technique and skill set likely matters. ECT as practiced in the general community has lower response rates (40%–60%) than the historical response rates (60%–80%) in the published literature from academic medical settings (Prudic et al. 2004).

ECT is unfortunately associated with acute and sometimes more chronic memory loss (Sackeim 2002). For all patients, memories of the events immediately around the procedure are lost. Memories of events prior to the ECT are impaired at first (retrograde amnesia) but return rapidly, within a matter of weeks. How frequently long-term memories are damaged is a matter of controversy. It is clear that several factors are important in determining potential cognitive damage with ECT, including the pulse width, electrode location, number of treatments, and any prior cognitive damage to the patient such as comorbid traumatic brain injury or mild dementia. Sackeim and colleagues measured cognitive effects of ECT in 347 patients treated at seven New York City hospitals. While almost all deficits had resolved at 6 months, some patients did have continued problems at 6 months, related to the type of ECT used. Those who had received bilateral ECT had three times the memory problems of an aged matched control sample who had not undergone ECT and who did not have a psychiatric illness (Sackeim et al. 2007). Because of these limitations and societal misperceptions, ECT is underused.

Shorter pulse widths have fewer cognitive side effects than the longer pulse widths used in traditional ECT (Sackeim et al. 2002). Sackeim and colleagues determined that the most efficient pulse width for an ECT pulse is about 0.25 milliseconds. They label this as "ultrabrief pulse width" and have shown that right unilateral ultrabrief pulse width ECT applied at a dose six times that needed to produce a seizure (seizure threshold) is as effective as older forms of ECT, with markedly less cognitive side effects (Sackeim et al. 2008). More than a seizure is needed for an antidepressant response. Electrode placement and optimal stimulation parameters, such as pulse width and suprathreshold dose, improve clinical response. Because of its improved cognitive side-effect profile and roughly similar efficacy, right unilateral (RUL) ultrabrief pulse ECT is now widely used.

Although ECT is the most effective acute treatment for depression, it is disappointing that at 6 months, many ECT patients who have responded or whose symptoms have remitted will relapse. For example, in one study, patients whose symptoms had remitted with ECT were

randomly assigned to receive placebo, nortriptyline, or nortriptyline plus lithium (Sackeim et al. 2001a). At 6 months, the relapse rate was 84% with placebo, 60% with nortriptyline, and 39% with nortriptyline and lithium. Some psychiatrists use maintenance ECT treatments every 3–5 weeks to prevent relapse, although formal studies with maintenance ECT are few. Some have even suggested using ECT for quick and acute antidepressant relief of a patient, and then using other, more durable brain stimulation techniques such as VNS, or even TMS, for longer-term relapse prevention.

Harold Sackeim began work many years ago to build supercharged TMS devices capable of reliably producing seizures in humans, reasoning that a TMS-induced seizure would be more focal and efficient than an ECT-induced seizure and spare much of the brain from receiving unneeded electricity (George and Wassermann 1994; Sackeim 1994). Magnetic seizure therapy (MST) has been shown feasible first in animals and now in patients (Lisanby et al. 2003). Patients have markedly less acute cognitive disruption from MST seizures than from traditional ECT. Whether MST has clinical antidepressant efficacy similar to that of conventional ECT is still not clear, and a multisite study is under way. In the most recent pilot study published to date, 13 patients participated in an open-label clinical trial of up to 18 treatment sessions with 100-Hz MST (Fitzgerald et al. 2013). At study end, only 5 of 13 (38%) met clinical response criteria, which is much less than one would expect with conventional ECT. There was an overall group reduction in depression severity, and no evidence of any impairment of orientation, memory, or other elements of cognition, after MST treatment. The major limitations of the study were its lack of sham control and the small study size. To date, no randomized clinical trials (RCTs) have been published that compare MST with ECT in terms of cognitive effects or clinical response. However, a recent small open-label study found no significant differences between MST-plus-pharmacotherapy versus ECT-plus-pharmacotherapy in 20 patients with treatment-resistant depression, both in antidepressant response (improvement of 50% in MADRS ratings statistically significant and of similar extent in both treatment groups) and in cognitive side effects (Kayser et al. 2011). Thus, MST may be a potential alternative to ECT, but larger clinical trials are needed to evaluate safety and efficacy.

Conventional ECT involves biphasic pulses or even sine waves. This means ECT is a form of alternating current, with either electrode producing the same effect. Alternating current offers limited control of intracerebral current paths. There is no direction to the current flow, and there are no positive or negative electrodes as with a battery (which uses direct current). Another variant of ECT involves delivering only monophasic pulses, or delivering direct current that cycles rapidly on and off and may create focal seizure activity. Researchers call this directional ECT *focal electrically administered seizure therapy*, or FEAST. By using a newer electrode configuration and unidirectional stimulation, this newer form of ECT can initiate seizures focally and specifically in the prefrontal cortex prior to secondary seizure generalization. Essentially, the area under the exiting anode on the right forehead becomes excited, and the seizure begins more focally, directly underneath the electrode. This approach has been effectively demonstrated in animal studies (Spellman et al. 2009). It is thought that seizure induction in pre-

frontal cortex is key for clinical efficacy, while seizure expression in medial temporal lobes causes amnestic effects. FEAST hypothetically preserves treatment efficacy while reducing memory side effects. A proof–of-concept clinical trial in depressed adult patients has shown that the cognitive side effects are mild, even when compared with right unilateral ultrabrief pulse ECT, and clinical effects are in the ballpark of conventional ECT (Nahas et al. 2013). More work is ongoing.

Transcranial Magnetic Stimulation

TMS is perhaps the most popular of the new techniques, because with TMS the skull does not need to be opened in order to focally stimulate, no seizure is needed, and to date there appear to be only limited side effects. Moreover, TMS can be used either as a research tool (to measure how excitable the brain is or to produce a temporary lesion) or as a therapy. TMS involves creating a powerful electrical current near the scalp. The electricity flowing in an electromagnetic coil on the scalp creates an extremely potent (near 1.5 Tesla) but brief (microseconds) magnetic field. The neat trick is that the TMS magnetic field enters the surface of the brain without interference from the skin, muscles, and bone. Although skin and bone act as resistors to impede electrical currents as stated above with ECT, magnetic fields pass unimpeded through the skull and soft tissue. In the brain, the magnetic pulse encounters nerve cells with resting potentials, and induces electrical current to flow. Thus, electrical energy is converted to magnetic fields outside the brain, which then pass through the skull and are converted back into electrical currents in the brain (Bohning 2000). TMS is thus sometimes called "electrodeless electrical stimulation."

The magnetic field acts as a trick to bridge the skull. Although magnetic fields do have biological effects on tissue, the vast majority of TMS effects likely derive not from the magnetic fields but rather from the induced electrical currents generated in the brain. TMS, with powerful but extremely brief magnetic fields, differs from constant low-field magnetic stimulation. TMS directly electrically tickles the brain, whereas constant weak magnets do not induce currents.

The amount of electricity needed to actually cause someone's thumb to move with a TMS coil varies considerably across different individuals. This amount, referred to as the *motor threshold* (MT), can be determined by either electromyography (EMG) of the thumb or index finger or by assessing visible movement or twitches in the intended muscles (Mishory et al. 2004; Pridmore et al. 1998). The MT changes depending on whether muscles are resting or active (tensed), and can also change with sleep deprivation and various medications (Paulus et al. 2008). About 60% of the variance between individuals in their MT is because of differences in the distance from the skull to the motor cortex (Kozel et al. 2000).

Brief History

The idea of using TMS, or something akin to it, to alter neural function goes back to at least the early 1900s. In 1902 Pollacsek and Beer, psychiatrists working down the street from Sigmund Freud in Vienna, filed a patent to treat depression and neuroses with an electromagnetic device that looks surprisingly like today's TMS machines (Beer 1902). The modern TMS era began in 1985 when Tony Barker and

colleagues, working in Sheffield, England, created a focal electromagnetic device with sufficient power to induce currents in the spine (Barker et al. 1985). They quickly realized that the device could also directly and non-invasively stimulate the human brain. Their device could only stimulate the surface of the brain, as the magnetic field falls off sharply with distance from the coil. Several researchers, including one commercial company, are creating more powerful TMS devices that stimulate deeper in the brain (Zangen et al. 2005). Unfortunately, it appears that the deeper the device stimulates, the broader or less focal the field must be. It is thus not yet possible with TMS to stimulate both deep in the brain and focally, as can be done with deep brain stimulation (DBS) (Deng et al. 2013).

A single pulse of TMS, applied over the motor cortex, produces a jerklike movement in the hand, arm, face or leg, depending on where the coil is positioned. A single pulse applied over the back of the brain can produce a *phosphene* (seeing light without light actually entering the eye). However, that is about the extent of the immediate positive effects that single-pulse TMS can produce. TMS pulses applied in rhythmic succession are referred to as *repetitive TMS*, or rTMS. rTMS can create behaviors not seen with single pulses, including the potential risk of causing an unintended seizure, particularly if the stimulation is conducted near the motor cortex. More than 20 seizures have occurred in the history of TMS use, out of an unclear total number of people stimulated (but easily representing more than 100,000 sessions) (Rossi et al. 2009). Since market introduction of the NeuroStar TMS Therapy system (Neuronetics, Inc., Malvern, PA) in October 2008, seven seizures have been reported with NeuroStar TMS Therapy, over a usage of more than 250,000 NeuroStar TMS treatment sessions, and more than 8,000 patients. In five of the seven seizures, patients were concurrently taking medications that may have altered the seizure threshold. The estimated risk of seizure under ordinary clinical use is thus approximately 1 in 30,000 treatments (0.003% of treatments) or 1 in 1,000 patients (0.1% of patients) (M. Demitrack, Neuronetics, personal communication, May 2013). This risk is less than or comparable to the risk of seizure associated with antidepressant medications. However, with medications a seizure can happen at any time, while all TMS seizures have occurred during stimulation, rather than later, and have been self-limited with no sequelae. rTMS seizures are more likely to occur with certain combinations of TMS intensity, frequency, duration, and interstimulus interval (Wassermann 1997). Current clinical treatment parameters stay well below these riskier combinations.

Research

Much research is under way to determine exactly which neurons TMS affects, and the cascade of neurobiological events that follow stimulation. We do know that different factors like gyral anatomy (how the brain is shaped), the distance from the skull to the brain (brain atrophy), and the orientation of nerve fibers relative to coil are all important.

One of the more interesting rTMS effects is that for brief periods of time, during stimulation, rTMS can block or inhibit a brain function. That is, rTMS over the motor area that controls speech can *temporarily* leave the individual speechless (motor aphasia), but only while the device is firing. Cognitive neuroscientists have used this knockout aspect, or "temporary lesioning" ability, of TMS to

re-explore and test the large body of information gleaned from years of studying stroke patients. Additionally, two pulses of TMS in quick succession can provide information about the underlying excitability of a region of cortex. This diagnostic technique, called *paired-pulse TMS*, can demonstrate the behavior of local interneurons in the motor cortex and serve as indirect measures of GABA or glutamate (Heide et al. 2006).

Single nerve cells form themselves into functioning circuits over time through repeated discharges. Externally stimulating a single nerve cell with low-frequency electrical stimulation can cause long-term depression (LTD), in which the efficiency of links between cells diminishes. High-frequency stimulation over time can cause the opposite effect, called *long-term potentiation* (LTP). These behaviors are thought to be involved in learning, memory, and dynamic brain changes associated with networks. A very exciting aspect of TMS research, and also the other brain stimulation techniques, is exploring whether one can use external brain stimulation to change brain circuits over time in a manner analogous to LTD or LTP. Many TMS studies have now shown inhibition or excitation lasting for up to several hours beyond the time of stimulation (Di Lazzaro et al. 2005). The clinical implications here are profound. If one could use brain imaging to identify the faulty network in the brain, one could then use TMS or other techniques to change learning and memory or to resculpt brain circuits. Some basic physiological studies indicate that you can only change a circuit while the behavior is ongoing and the cells involved in the various neural pathways are acting as a circuit (Stanton and Sejnowski 1989). It is an important question whether TMS should be delivered while patients are thinking about important topics or using a certain muscle. Thus, research is now focusing on combining TMS with modified forms of cognitive-behavioral therapy or physical medicine rehabilitation.

Animal Studies With TMS

Animal and cellular studies with TMS reinforce that it is a powerful technique able to alter neuronal function. One stumbling block in using TMS in animals is that it is hard to make TMS coils that are the same relative size to most animals as in humans. Small coils explode. Thus, most animal TMS studies, especially small-animal studies, have not really used focal TMS as it would be used in humans. Nevertheless, studies have shown that rTMS enhances apomorphine-induced stereotypy and reduces immobility in the Porsolt swim test (Fleischmann et al. 1996), induces electroconvulsive shock (ECS)–like changes in rodent brain monoamines, and promotes beta-adrenergic receptor binding and immediate early gene induction (Ben-Shachar et al. 1997). Most recently, researchers have found that TMS can induce neurogenesis (Pope and Keck 2001).

Combining TMS With Functional Imaging

Not only can TMS be used as a therapeutic tool, but when combined with functional imaging, it has diagnostic and prognostic potential to guide clinical treatment by elucidating differential brain effects with various TMS parameters. Since it appears that TMS at different frequencies has divergent effects on brain activity, combining TMS with functional brain imaging will better delineate not only the behavioral neuropsychology of various psychiatric syndromes but also some of the pathophysiological circuits in the brain.

In contrast to imaging studies with ECT, which have found that ECT shuts off global and regional activity following the seizure (Nobler et al. 2001), most studies using serial scans in depressed patients undergoing TMS have found increased activity in the cingulate and other limbic regions (Teneback et al. 1999). However, two studies have now found divergent effects of TMS on regional activity in depressed patients, determined both by the frequency of stimulation and the baseline state of the patient (Mitchell 2002). That is, for patients with global or focal hypometabolism, high-frequency prefrontal stimulation increases brain activity over time. But the opposite is happening as well. Conversely, patients with focal hyperactivity have reduced brain activity over time following chronic daily low-frequency stimulation. However, these two small-sample studies have numerous flaws. They simultaneously show the potential, and the complexity, surrounding the issue of how to use TMS to change activity in defined circuits. They also point out an obvious difference with ECT, where the net effect of the ECT seizure is to decrease prefrontal and global activity (Nobler et al. 2001).

When a neuron fires or discharges, different neurotransmitters are released in the synaptic cleft. Thus, the brain stimulation methods are in one view simply "focal pharmacology." These links between brain stimulation methods and traditional pharmacological views of the psychiatric illnesses have been highlighted by studies using radioligands. Baeken and colleagues examined the neurobiological impact of 10 rTMS sessions applied to the left dorsolateral prefrontal cortex (DLPFC) on postsynaptic 5-HT_{2A} receptor binding indices measured with ^{123}I-5-I-R91150 single photon emission computed tomography (SPECT). Compared with the control group, patients displayed significantly less bilateral dorsolateral prefrontal cortical and significantly higher left hippocampal baseline 5-HT_{2A} receptor binding indices. Successful high-frequency rTMS treatment correlated positively with 5-HT_{2A} receptor binding indices in the DLPFC bilaterally and correlated negatively with right hippocampal 5-HT_{2A} receptor uptake values. These results indicate that high-frequency rTMS treatment affects the serotonergic system within the prefrontal cortex as patients respond (Baeken et al. 2011).

Despite initial concerns, one can actually perform TMS within a magnetic resonance imaging (MRI) scanner, which is itself a huge magnet and is constantly on (Bohning 2000; Bohning et al. 1998). Work with this interleaved TMS/functional MRI technology has shown that prefrontal TMS at 80% MT produces much less local and remote blood flow change than does TMS at 120% MT (Nahas et al. 2001). Strafella and colleagues used positron emission tomography to show that prefrontal cortex TMS causes dopamine release in the caudate nucleus (Strafella et al. 2003) and has reciprocal activity with the anterior cingulate gyrus (Paus et al. 2001). Our group at MUSC (George et al. 1999), as well as others in Scotland (Shajahan et al. 2002) and Australia (Mitchell 2002), have all shown that lateral prefrontal TMS can cause changes in the anterior cingulate gyrus and other limbic regions in depressed patients. It is thus clear that TMS delivered over the prefrontal cortex has immediate effects in important subcortical limbic regions. TMS over different aspects of the prefrontal cortex (lateral vs. medial) can produce different secondary activations (Figure 15–1). This highlights the notion that stimulating the cortex with TMS really is "opening a window" to different

cortical-subcortical networks. The initial TMS effect on cortex and the secondary synaptic changes in other regions likely differ as a function of mood state, cortical excitability, and other factors that would change resting brain activity. Combining TMS with functional imaging will likely continue to be an important method for understanding TMS mechanisms of action. Combinational TMS/imaging will likely also evolve to be an important neuroscience tool for researching brain connectivity (George and Bohning 2002).

Therapeutic Uses of TMS

Depression

Although more work is needed, certain brain regions have consistently been implicated in the pathogenesis of depression and mood regulation. These include the medial and dorsolateral prefrontal cortex, cingulate gyrus, and other regions commonly referred to as *limbic* (amygdala, hippocampus, parahippocampus, septum, hypothalamus, limbic thalamus, insula) and *paralimbic* (anterior temporal pole, orbitofrontal cortex). A widely held theory over the last 20 years has been that depression results from a dysregulation of these prefrontal cortical and limbic regions (George et al. 1994, 1995a, 1996; Mayberg et al. 1999). The very first uses of TMS as an antidepressant were not influenced by this regional neuroanatomic literature, and stimulation was applied over the vertex (Beer 1902; Grisaru et al. 1994; Kolbinger et al. 1995). However, working within the prefrontal cortical limbic dysregulation framework outlined above, and realizing that theories of ECT action emphasize the role of prefrontal cortex effects (Nobler et al. 1994), in 1995 George and colleagues performed the first open trial of daily prefrontal TMS as an antidepressant (George et al. 1995). This was followed immediately by a cross-over, double-blind study (George et al. 1997). The reasoning was that chronic, frequent subconvulsive stimulation of the prefrontal cortex over several weeks might initiate a therapeutic cascade of events both in the prefrontal cortex and in connected limbic regions, thereby causing the dysregulated circuits to rebalance and normalize, alleviating depression symptoms (George and Wassermann 1994). The imaging evidence previously discussed now shows that this hunch was largely correct—prefrontal TMS sends direct information to important mood-regulating regions such as the cingulate gyrus, orbitofrontal cortex, insula, and hippocampus. Thus, beginning with these prefrontal studies, modern TMS was specifically designed as a focal, nonconvulsive, circuit-based approach to therapy.

In 2008, the NeuroStar TMS Therapy system (Neuronetics, Inc., Malvern, PA) received FDA clearance for the treatment of adult patients with major depressive disorder (MDD) who have failed to receive satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode. FDA clearance was based on a large, multisite, sham-controlled randomized study that showed that daily prefrontal TMS was a safe and effective treatment for certain patients with major depression. The observed effect sizes in both the original study population (N=301 [O'Reardon et al. 2007]) and the subset of patients who met the FDA-approved indication for use of the NeuroStar TMS Therapy system (N=164 [Demitrack and Thase 2009]) are of similar or greater magnitude than those observed with the majority of currently approved antidepressant medication treatments. It is likely that TMS as is now done is less effective than ECT as is now done, although this is an

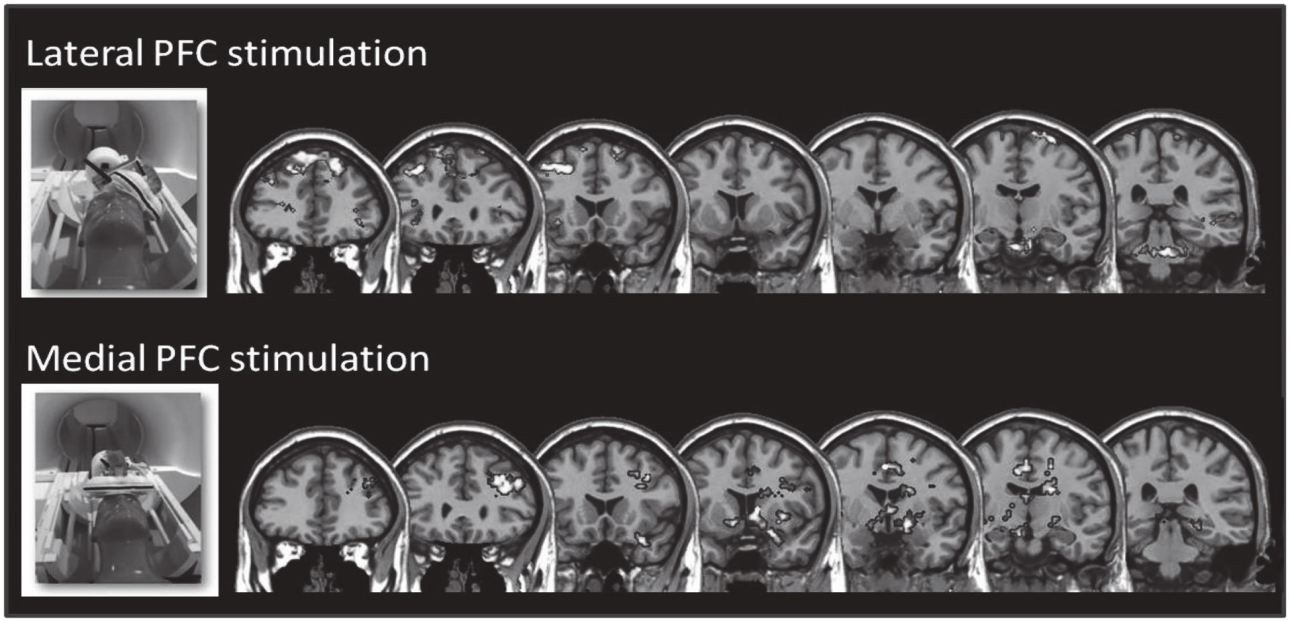

FIGURE 15–1. **Group BOLD functional magnetic resonance imaging activation maps, using an optimized interleaved transcranial magnetic stimulation (TMS)/BOLD sequence in two cortical targets to examine the differential activation of lateral and medial neural circuits, which are known to be important in drug abuse and/or mood regulation.**

Interleaved TMS/BOLD imaging data were acquired for 10 healthy individuals who received TMS in two runs with the coil positioned over the 1) DLPFC and 2) mPFC. DLPFC TMS was associated with a significant elevation of BOLD signal in multiple dorsal cortical areas, whereas mPFC TMS was associated with a significant elevation of BOLD signal in multiple medial and limbic subcortical areas. These preliminary data demonstrate that cortical TMS produces secondary effects deeper in the brain. TMS is thus opening cortical windows into different brain circuits, depending on the connectivity pattern of the cortical region being stimulated.

Source. These images derive from work by Dr. Colleen Hanlon and colleagues at MUSC (Li et al. 2004b; Hanlon and Canterberry 2012).

area of controversy and needs further study. Of note, it is the potential TMS devices that receive FDA approval, not "TMS" itself per se.

George and colleagues, in a 190-patient National Institute of Mental Health–sponsored multisite, randomized controlled trial (called OPT-TMS) demonstrated that rTMS, as drug-free monotherapy, produced statistically significant antidepressant effects with a remission rate four times that seen with sham patients (George et al. 2010). This study provided industry-independent Class I evidence of safety and efficacy in a well-studied and carefully controlled cohort. Two additional publications resulted from this trial. McDonald et al. (2011) reported on an open-label extension phase of this trial. They found that 43 of 141 (30.5%) patients who enrolled in the open phase study eventually met criteria for remission. Some patients took up to 6 weeks to achieve full remission (McDonald et al. 2011). Most recently Mantovani et al. (2012) reported on the 3-month durability of the TMS antidepressant response in this trial. Of the 50 patients who experienced remission of symptoms and agreed to participate in follow-up, at 3 months, 29 of 50 (58%) were classified as in remission (Hamilton Rating Scale for Depression [HRSD]–24 ≤10), two of 50 (4%) as having had a partial response (30%≤HRSD-24 reduction <50% from baseline), and 1 of 50 (2%) as having met criteria for relapse (Mantovani et al. 2012).

These studies demonstrate that daily left prefrontal TMS for 3–6 weeks has antidepressant effects that are significantly greater than sham, and that these effects in the open phase trial are clinically meaningful (30% remission). Even more importantly, the outcomes are at least as robust as next-choice antidepressant medication; the procedure was found to be safe and well tolerated, with a low incidence of treatment discontinuation; and the therapeutic effects, once obtained, are reasonably durable.

Most recently, another TMS device manufacturer, Brainsway (Jerusalem, Israel), has completed an international RCT and has gotten FDA approval for marketing their device to treat depression. The results of this trial have not been published yet, but a Brainsway press release ("Brainsway Received FDA Approval" 2013), reporting on early results of their double-blind, multicenter controlled trial of the system, indicated that after 5 weeks of treatment, 30.4% of patients in the active treatment group achieved remission from depression, compared with 14.5% of the sham treatment control group (P=0.0148). (Remission was defined as a HRSD–21 score of less than 10.)

Other recent studies have explored whether TMS is effective in modern clinical practice. In a multi-site observational study in 307 real-world patients getting care with TMS in clinical practice settings (Carpenter et al. 2012), the individuals described had received an average of two antidepressant treatments of adequate dose and duration without successful improvement in their current episode of depression, and were markedly ill at enrollment. With an acute course of TMS treatments (average 28 treatment sessions), symptom severity ratings decreased significantly, regardless of the metric used for assessment. With categorical outcomes, 58% of the subjects were responders on the primary outcome measure (CGI-S), and 37% had reached remission, with similar findings on the secondary measures. This new study of TMS outcomes, as delivered in real-world practices to care-seeking patients, adds additional evidence to the effectiveness of TMS in patients with

treatment-resistant depression. This therapy appears to work in real-world settings and not just in rigorous clinical research trials. Unlike with many therapies in medicine, there does not appear to be an efficacy/effectiveness gap with prefrontal TMS for acute depression.

Findings from another observational study of how TMS works in real-world settings were recently published. Connolly et al. (2012), from the University of Pennsylvania, reported data from the first 100 patients treated at their university-based TMS clinical service following FDA approval. As in the Carpenter et al. study, their cohort involved patients with treatment-resistant depression, but with a mean of three failed adequate antidepressant trials in the current episode. Thirty-one individuals had received prior lifetime ECT, and 60% had a history of psychiatric hospitalization. The Clinical Global Impression–Improvement (CGI-I) response rate was 50%, and the remission rate was 25% at 6 weeks. The HRSD response and remission rates were 41% and 35%, respectively. Forty-two patients (49%) entered 6 months of maintenance TMS treatment. Sixty-two percent (26 of 42 patients) had maintained their responder status at the last assessment during the maintenance treatment. TMS treatment was well tolerated, with a discontinuation rate of 3% in the acute treatment phase. No serious adverse events related to TMS were observed during acute or maintenance treatment. The authors concluded that adjunctive TMS was safe and effective in both acute and maintenance treatment of patients with treatment-resistant depression.

Unresolved Issues. Although the literature suggests that prefrontal TMS has an antidepressant effect greater than sham, and that the magnitude of this effect is in the range of other antidepressants, many issues are not resolved. Work done to date has shown substantial evidence that prefrontal TMS produces immediate (George et al. 1999; Li et al. 2002) and longer term (Teneback et al. 1999) changes in mood-regulating circuits. Thus, the original hypothesis about its antidepressant mechanism of action is still the most likely explanation. What remains unclear is which specific prefrontal or other brain locations might be the best for treating depression, and whether this can be determined with a group algorithm or needs individual imaging guidance. For the most part, the coil has been positioned using the rule-based algorithm to find the prefrontal cortex that researchers, including one of the present authors (M.S.G.), developed in the early studies (George et al. 1995b). However, this method was shown to be imprecise in the particular prefrontal regions stimulated directly underneath the coil, depending largely on the subject's head size (Herwig et al. 2001). Additionally, most studies have stimulated patients at or above the patient's MT. There is now increasing recognition that higher intensities of stimulation are needed to reach the prefrontal cortex, especially in elderly patients, in whom prefrontal atrophy may outpace that of the motor cortex, where the MT is measured (Kozel et al. 2000). There are a few case series suggesting that one can use weekly or monthly rTMS as a maintenance treatment after someone has responded acutely (Nahas et al. 2000; Li et al. 2004a; O'Reardon et al. 2005).

Other active areas of research involve exploring whether one can combine TMS with some behavioral therapy to increase efficacy (Vedeniapin et al. 2010), or whether one can deliver higher doses or density of treatment to speed response (Holtzheimer et al. 2010).

Another interesting development with TMS is different coil designs (Deng et al. 2013; Huang et al. 2009). Most studies described in this chapter used a figure-eight coil, which is quite focal in terms of the field created in the brain (Roth et al. 1991). Abraham Zangen and his colleagues (Zangen et al. 2005) in Israel (Brainsway) have designed a series of different TMS coils that penetrate much deeper and broadly into the brain than do traditional coils (Zangen et al. 2005). It is unclear whether and to what degree and in what conditions a deeper or broader TMS coil would have advantages over a more superficial coil. Theoretically, if one is not using individual structural or functional MRI scans to guide the TMS coil placement, a broader coil would have a higher probability of stimulating mood-regulating circuits than would a more precise coil. That is, when a target cannot be seen, a shotgun fired into the woods has a higher probability of hitting prey than does a rifle. It simply covers a broader area. Are there specific prefrontal regions that each person uses to regulate his or her mood? If so, how could we best image these regions? Or, is regulation a function of broad areas of the cortex? In this case a broader, less focal coil might be more effective. More research is needed into this most important question with respect to using TMS to treat depression and other psychiatric disorders.

Other Psychiatric Conditions

TMS has also been investigated as a possible treatment for a variety of neuropsychiatric disorders. In general, the published literature in these conditions is much less extensive than for TMS as an antidepressant, and therefore conclusions about the clinical significance of effects must remain tentative until large-sample studies are conducted.

Pain

Mood-regulating centers in the brain overlap significantly with the neural pathways involved in pain regulation, especially the regions involved in determining whether a pain is really bothersome. Thus, some researchers have begun exploring whether TMS might have a therapeutic role in treating acute or chronic pain. There are exciting reports that TMS over either prefrontal cortex or motor cortex can acutely decrease pain in healthy adults or patients with chronic pain (André-Obadia et al. 2006; Pridmore and Oberoi 2000; Short et al. 2011). A recent RCT found that a single 20-minute session of left prefrontal rTMS given to patients in the recovery room following surgery reduced self-administered morphine use by 40% (Borckardt et al. 2006b). In the lab, a 20-minute dose of prefrontal TMS can also increase pain thresholds. This effect is blocked in healthy volunteers by pretreatment with naloxone, suggesting that opiate receptors play a necessary role in the antinociceptive effects of TMS (Taylor et al. 2012). This complicated challenge and pharmacological blockade study in the MRI scanner suggests that the prefrontal TMS is activating conventional pain pathways and that the naloxone blocks activity in the mid-brain.

Vagus Nerve Stimulation

TMS is non-invasive, focal (largely limited to different cortical sites), and intermittent. VNS is in some sense the opposite of TMS, as it is invasive, requiring surgical implantation of a device in the chest wall and a wire in the neck. The brain region stimulated is always the same initial

route—the vagus nerve in the neck. It is also a permanent implant that cannot be removed without surgery. VNS has been approved for almost 15 years as a treatment for epilepsy, and was FDA approved in 2005 for chronic use in patients with treatment-resistant depression.

Brief History

It seems obvious to ask whether and to what degree stimulation of a cranial nerve has effects on brain function. Thus, throughout the past century, researchers have investigated whether stimulation of cranial nerves might have observable brain effects. Of all the cranial nerves, with the exception of CN I for olfaction, the vagus nerve (CN X), has been the most intriguing, and arguably the most misunderstood. The vagus nerve helps regulate the body's autonomic functions, which are important in a variety of emotional tasks. For reasons that are unclear, most people are more familiar with the vagus nerve's efferent functions, where it serves as the messenger for signals *from the brain* to the viscera. Traditionally, the vagus nerve has been considered a parasympathetic efferent nerve, controlling and regulating autonomic functions such as heart rate and gastric tone. The afferent role of the vagus has been underemphasized in the traditional literature. The vagus is actually a mixed nerve composed of about 80% afferent sensory fibers carrying information *to the brain* from the head, neck, thorax, and abdomen (Foley and DuBois 1937).

For the past 100 years several different researchers have convincingly demonstrated the extensive projections of the vagus nerve via its sensory afferent connections in the nucleus tractus solitarius (NTS) to diverse brain regions (Zardetto-Smith and Gray 1990). Reasoning in part from this body of literature, Jake Zabara discovered an anticonvulsant action of VNS on experimental seizures in dogs (Zabara 1992). Zabara hypothesized that VNS could prevent or control the motor and autonomic components of epilepsy. Penry and others ushered in the modern clinical application of VNS in 1988 using an implanted device to treat epilepsy (Penry and Dean 1990).

Although the route of entry into the brain is constrained, VNS offers the potential for modulating and modifying function in many brain regions, through trans-synaptic connections (George et al. 2000). The incoming sensory (afferent) connections of the vagus nerve provide direct projections to many of the brain regions implicated in neuropsychiatric disorders. These connections provide a basis for understanding how VNS might be a portal to the brain stem and connected limbic and cortical regions. These pathways likely account for the neuropsychiatric effects of VNS, and they invite additional theoretical considerations for potential research and clinical applications. Functional imaging studies in patients with implanted VNS stimulators have largely confirmed this important neuroanatomy of the vagus nerve (Bohning et al. 2001; Chae et al. 2003; Conway et al. 2006; Henry et al. 1998).

VNS Methods

The broad term *vagus nerve stimulation* refers to any technique used to stimulate the vagus nerve, including the approach used in studies in animals in which the vagus was accessed through the abdomen and diaphragm. However, for nearly all human studies, the term refers to stimulation of the left cervical vagus nerve using a commercial device. There are groups

studying whether one can stimulate the vagus nerve through a cutaneous branch in the earlobe (Busch et al. 2013; Stefan et al. 2012), or through non-invasive stimulation through the neck (Miner et al. 2012). These approaches have not been used in the clinical trials discussed below, which rely on the implanted device and stimulation of the cervical vagus.

Cervically implanted VNS has been commercially available for the treatment of resistant partial onset seizures in Europe since 1994, and in the United States since 1997. VNS resembles implanting a cardiac pacemaker. In both VNS and cardiac pacemakers, a subcutaneous generator sends an electrical signal to an organ through an implanted electrode. With VNS, the electrical stimulation is delivered through the generator, an implantable, multi-programmable bipolar pulse generator (about the size of a pocket watch) that is implanted in the left chest wall to deliver electrical signals to the left vagus nerve through a bipolar lead. The electrode is wrapped around the vagus nerve in the neck and is connected to the generator subcutaneously.

The VNS implantation surgery is typically an outpatient procedure, most commonly but not exclusively performed by neurosurgeons. The VNS generator can be controlled by a personal computer or PDA connected to an infrared wand. As a safety feature, the VNS generator is designed to shut off in the presence of a constant magnetic field. Each patient is thus given a magnet that, when held over the pulse generator, turns off stimulation. When the magnet is removed, normal programmed stimulation resumes. This allows patients to control and temporarily eliminate stimulation-related side effects during important behaviors like public speaking (voice tremor) or heavy exercising (mild shortness of breath).

Therapeutic Uses of VNS

Epilepsy

VNS has been most extensively studied as a treatment for epilepsy. Two double-blind studies have been conducted in patients with epilepsy, with a total of 313 with treatment-resistant epilepsy who completed the trial (Ben-Menachem et al. 1994; Handforth et al. 1998). In this difficult-to-treat group, the average decline in seizure frequency was about 25%–30% compared with baseline.

Most epilepsy patients with VNS have not been able to reduce or withdraw antiepileptic medications. Thus VNS, as now delivered, has not been shown to be a substitute for anticonvulsant medications, although in some patients, the dosage levels or number of anti-epileptic medications has been decreased with the addition of VNS. VNS is increasingly being used in children with epilepsy, in part because of its lack of negative cognitive effects, which are common to other anticonvulsants (Helmers et al. 2001).

There are several different programmable variables in determining how to deliver VNS. These "use parameters" include the pulse width of the electrical signal (130, 250, 500, 750, 1,000 microseconds), the intensity (0.25–4 mA is clinically tolerated), the frequency (1–145 Hz), length of stimulation (7–270 seconds), and length of time between trains of stimuli (0.2 seconds–180 minutes). In general, the initial epilepsy use parameter settings were those found to stop seizures acutely in animal models. The initial human epilepsy studies compared efficacy in two groups on the basis of different use parameters. There was a high-stimulation group (30 Hz, 30 seconds on, 5 minutes off, 500-microsecond pulse width) and a low-stimulation group (1 Hz, 30 seconds on, 90–180 minutes off, 130-microseconds pulse width).

The majority of the VNS epilepsy efficacy and safety data come from trials with use parameters similar to those used in the high-stimulation group. Similarly, most of the data from other neuropsychiatric disorders (depression, anxiety) involve VNS at use parameters similar to those in the initial epilepsy studies. It is difficult to imagine that these use parameters are the maximally effective choices or that the same parameters work equally well in all conditions and all patients. Epilepsy physicians commonly switch nonresponding patients to use parameter settings that are different from their current settings. However, there has been no clear demonstration that changing settings improves efficacy. Further work understanding the translational neurobiology of these use parameter choices, and how they relate to clinical symptoms, is the key area for future growth of the field.

Depression

It has long been recognized in psychiatry that anticonvulsant medications (e.g., carbamazepine) and devices (e.g., ECT) have mood-stabilizing or antidepressant effects. In early 1998, there were several lines of evidence to suggest that VNS might have antidepressant effects. Anecdotal reports of mood improvement in VNS-implanted epilepsy patients, knowledge of vagus function and neuroanatomy, brain imaging studies, work in animals, and cerebrospinal fluid studies all supported an initial pilot clinical trial in treatment-resistant depression (George et al. 2000).

An initial open study of VNS for chronic or recurrent treatment-resistant depression involved four sites and 30 subjects (Rush et al. 2000), with a later extension of 30 more subjects to clarify the effect size and look for response predictors (Sackeim et al. 2001c). The study design involved selecting patients with a treatment-resistant, chronic, or recurrent major depressive episode (MDE) (unipolar or nonrapid cycling bipolar) and then adding VNS to a stable regimen of antidepressant medications or no antidepressant medications. No stimulation was given for the first 2 weeks following implantation, creating a single-blind placebo phase and allowing for surgical recovery. All patients met eligibility criteria by having failed to respond in at least two adequate treatment trials in the current episode.

VNS therapy was provided for 10 weeks with medications held constant. Of 59 completers (1 patient improved during the surgical recovery period), the response rate was 30.5%. VNS was well tolerated in this group, with side effects similar to those encountered by epilepsy patients. The most common side effect was voice alteration or hoarseness, in 60.0% (36/60), which was generally mild and related to the intensity of the output current. There were no adverse cognitive effects (Sackeim et al. 2001b). The only response predictor was prior antidepressant treatment resistance. VNS as used in this open study was more effective in depressed patients who were less treatment resistant.

These encouraging initial results served as the basis for a U.S. multi-site double-blind trial of VNS for chronic or recurrent, low to moderate treatment-resistant depression. In this trial, active VNS failed to show a statistically significant difference in acute response from the sham condition (Rush et al. 2005). The sham response rate was 10%, with the active response 15%. This difference was not significant given the small sample size (approximately 200). The longer term response rates for VNS-implanted depressed patients were encouraging (Nahas et al. 2005) and appear better than

what would be expected in this population (Rush et al. 2006). A parallel but nonrandomized comparison found that patients with VNS implanted had better outcomes at 1 year than a group receiving treatment as usual (George et al. 2005). These data served as the basis for FDA approval of VNS for the chronic (not acute) treatment of chronic recurrent depression. Thus, VNS is FDA approved, although there is no double-blind, randomized controlled evidence for VNS as an antidepressant in patients with depression. There are, however, open (Harden et al. 2000) and double-blind (Elger et al. 2000) studies showing that VNS has antidepressant effects in epilepsy patients with comorbid depression. A European long-term study found open-label results similar to the US study (Schlaepfer et al. 2008b). By 3 months of VNS, response rates (≥50% reduction in baseline scores) had reached 37%, and remission rates (HRSD-28 score<10) had reached 17%. Response rates increased to 53% after 1 year of VNS, and remission rates reached 33%. Response was defined as sustained if no relapse occurred during the first year of VNS after response onset; this criterion was met in 44% of patients. The median time to response was 9 months.

Optimal settings and patient selection are the focus of further work. Recent trial results suggest that moderate and higher dose VNS parameter settings have better response durability than lower settings (Aaronson et al. 2013). In another report, baseline cerebral metabolic activity predicted antidepressant response to VNS (Aaronson et al. 2013; Conway et al. 2012a, 2012b).

Thus, VNS for depression does not appear to be a useful acute treatment, but rather appears to help patients with treatment-resistant depression chronically, with long-term improvements (Nahas et al. 2005). Unfortunately, only 30% of implanted patients have clinically meaningful improvements, and there are no proven methods of choosing before implantation who will later respond (Conway et al. 2012b).

Noninvasive forms of VNS, either through the skin over the neck or through a branch of the vagus that projects to the ear, are under study. These non-invasive approaches may rekindle research for VNS for a variety of diseases, including epilepsy (Stefan et al. 2012), pain perception (Busch et al. 2013), and septic shock (Zhao et al. 2012).

Anxiety

As reviewed at the start of this section, the sensory afferent nerve fibers that VNS stimulates in the vagus travel to the brain and terminate in the nucleus solitary tract (NTS). These fibers are the primary means by which the brain receives information from the organs within the gut and diaphragm. From there, information travels to the locus coeruleus, the primary site of all norepinephrine fibers in the brain. Norepinephrine has long been considered to be a critical neurotransmitter system involved in the pathogenesis and regulation of anxiety. A device that directly stimulates this norepinephrine control site would likely have important effects on anxiety. A small clinical trial of VNS in anxiety patients found promising results (George et al. 2008).

Pain

Some information about pain, especially visceral pain, travels through the vagus nerve. A recent study showing changes in pain perception as a function of different VNS settings hints at the promise of using VNS for some form of pain modulation (Borckardt et al. 2005, 2006a).

In conclusion, VNS has an important role in the treatment of epilepsy. How-

ever, the only clinical effects that have been shown with double-blind studies are in epilepsy for seizure control and depression occurring in the setting of epilepsy. Yet, VNS is FDA approved only for depression. There are many areas where more information would facilitate its adoption. Compared with talking therapy, medications, and even ECT, VNS requires a different approach to treating depression. Whereas other treatments can be begun and sampled and then easily abandoned if not effective, VNS, with the installation of an implant, requires careful consideration prior to initiating therapy. There is interest, but no data, about using a non-invasive method of VNS prior to a permanent implant to potentially increase the certainty that implanted patients would be responders. Additionally, because of the relatively large initial capital costs of implanting a VNS generator, data are needed to convince payers that VNS is cost-effective. An initial implantation fee of around $30,000 (device and surgery) is about equal to 1 week of hospitalization or a course of outpatient ECT. VNS would thus be cost-effective for those recurrent chronically ill patients in whom implantation results in clinical improvements that eliminate the need for hospitalization, ECT, or more frequent and aggressive outpatient medication management.

Another radical difference between VNS and medication treatments is that VNS facilitates almost 100% adherence. The device, once implanted, cycles on and off without problems for several years. Several studies have shown that even the best patients skip and forget medications, with resultant problems in their clinical course. VNS is thus a most interesting new approach to treating depression, but more information is critically needed.

Deep Brain Stimulation

The most invasive of all the brain stimulation techniques is deep brain stimulation (DBS), in which an electrode is implanted deep within the brain, connected to a generator located in the chest wall that sends constant electrical current into the brain. Theoretically, DBS electrodes can be removed without destroying large amounts of the brain, and thus DBS has less morbidity and mortality than resective brain surgery.

Brief History

The first modern use of DBS involved treatment for Parkinson's disease tremor (Limousin et al. 1995) and more recently dystonia (Halpern et al. 2007; Tisch et al. 2007). DBS for these movement disorders involves placing the electrodes at one of two different target locations—the subthalamic nucleus (STN) or the globus pallidus (interna) (GPi). In this use of DBS, the electrodes are turned on constantly at high frequency (>130 Hz). The neuropsychiatric use of DBS began with work for treatment-resistant OCD patients, with the electrodes implanted at the anterior limb of the internal capsule, bilaterally (Greenberg et al. 2000; Nuttin et al. 1999, 2003). This DBS placement followed the neurosurgical literature, in which it had been demonstrated that focal ablation of these communicating fibers sometimes resulted in therapeutic treatment. Although positive effects were found in OCD symptoms, mood improvements were also seen (Gabriëls et al. 2003; Greenberg et al. 2000, 2003). These open case series results were presented by a DBS manufacturer (Medtronic) to the FDA for potential approval of a humanitarian device exemption (HDE) for treatment-resistant OCD. This HDE was granted in February 2009 for

DBS to "be used in conjunction with medications for the treatment of chronic, treatment resistant adult OCD patients to aid in the management of the symptoms."

Because the majority of studies published thus far on DBS for OCD have different brain targets and designs, comparison of results across studies is quite difficult (Greenberg et al. 2010). One study of unilateral (right) nucleus accumbens DBS reported a partial response in 5 of 10 patients and a full response in 1 patient at 1-year follow-up (Huff et al. 2010). A ventral internal capsule/ventral striatum (VC/VS) DBS efficacy study reported a response in 4 of 6 patients at 12-month follow-up (Goodman et al. 2010). A second bilateral VC/VS pilot study assessing long-term outcomes in four adult patients receiving DBS for refractory OCD found a 33.06% decrease in OCD severity at 15-months follow-up (Tsai et al. 2012). In a bilateral nucleus accumbens DBS study, 9 of 16 patients responded to treatment, with an average 72% decrease on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). This is the largest follow-up decrease in Y-BOCS scores) published to date (Denys et al. 2010). A 2011 literature review identified a total of nine open (case) studies and seven controlled studies with a blinded on–off phase. This review found that 34 of 63 patients undergoing DBS for OCD experienced a 35% improvement in Y-BOCS scores but asserted that the optimal brain target, as well as the mechanism of action of DBS for OCD, remains unclear (de Koning et al. 2011).

Uses of DBS

Depression

Expanding on the positive mood effects observed in OCD patients, the Brown University group used DBS at the same target sites (anterior limb of the internal capsule [ALIC]) in patients with treatment-resistant depression. Fifteen patients received implants in an open-label fashion with the DBS electrodes as an adjunctive treatment. In this highly treatment-resistant cohort, mean HRSD scores dropped significantly over 6 months (from 33 at entry to 17.5 at 6 months), and there was one case of emergent hypomania (Malone et al. 2009). Medtronic started a large RCT in treatment-resistant depression at this anatomical site. The study was not finished, and results have not been published.

Following a different line of reasoning (Laitinen and Vilkki 1972), another group has implanted electrodes in the white matter fiber tracts next to the rostral anterior cingulate (CG25) (Mayberg et al. 2005). In 20 patients with treatment-resistant unipolar depression, CG25 DBS produced a reduction in HRSD scores from 24.4 at entry to 12.6 by 12 months. Three patients had their devices removed before 12 months (Lozano et al. 2008; McNeely et al. 2008). (One manufacturer, St. Jude, is in the middle of a large multisite RCT of stimulation in this region. Approximately 100 patients have been studied as of this writing.)

Following yet a different line of reasoning (Schlaepfer et al. 2008a), another group is investigating effects of bilateral high-frequency stimulation to the nucleus accumbens. Acute anti-anhedonic and antidepressant effects have been demonstrated (Schlaepfer et al. 2008a), and recent results in 10 patients with very treatment-resistant depression demonstrated response in half of the patients (Kayser et al. 2009). One patient who had achieved remission committed suicide during a relapse. The same group bilateral stimulated the medial forebrain bundle of 7 patients with treatment-resistant depression. These small sample results suggest a more robust (6 of 7 were

responders, 4 of 7 were remitters) and rapid (in 1 week) antidepressant response than observed with nucleus accumbens or anterior cingulate cortex stimulation at lower currents (Schlaepfer et al. 2013).

Although these studies are small in sample size (20, 15, 10, and 7 patients, respectively), their results are very important in light of the fact that the patients studied had not responded to all other potential treatments.

Another form of invasive brain stimulation is *epidural cortical stimulation*, which is based on cortical regulation of subcortical, limbic regions. In one pilot study, two anterior and two midlateral cortical stimulation leads were implanted in five patients with treatment-resistant depression. At 7-month follow-up, there was a 60% improvement in HRSD, and three patients had experienced remission of symptoms. One patient's left hemisphere leads were explanted at 12 weeks postsurgery because of a scalp infection. Thus, the possible targets of implanted brain stimulation may not solely be subcortical (Nahas et al. 2010).

Other Indications

There are case reports and ongoing studies of DBS in the treatment of Gilles de la Tourette syndrome, substance abuse, addictions, obesity, and schizophrenia.

Adverse Events

In DBS, side effects are related to either the operation itself (e.g., bleeding, local infections at the implantation site or generator location) or the stimulation (e.g., increase of mood, anxiety). Fortunately, the safety of the stereotactic operation technique has been improved in the last years with the help of improved structural neuroimaging. Rates of hemorrhage of DBS surgeries are between 0.2% and 5% (Greenberg et al. 2003; Kayser et al. 2009; Lozano et al. 2008).

Continued research in DBS for neuropsychiatric disorders is needed. DBS, although it is less invasive than ablative surgery, nevertheless is the most invasive of the brain stimulation therapies. Thus, clinicians need to be especially cautious in potential clinical use. Because of the high vulnerability of psychiatric patients, the lack of extensive short- and long-term data about effectiveness and adverse effects, and the haunting history of psychosurgery, the use of DBS for psychiatric indications still remains controversial and bears several specific ethical concerns that have only rarely been addressed so far.

For the indications of OCD and chronic pain, DBS at appropriate targets is clinically indicated but should only be performed by well-trained neurosurgeons in well-screened patients referred from a treating psychiatrist who have been aggressively treated with other options and have not responded. Psychiatrists should be the clinicians making the recommendation and providing follow-up. In general, DBS patients must also receive a positive second opinion recommending DBS from a trained and certified psychiatrist who is not related to the research group or referring psychiatrist. As a general guideline it is also appropriate to consider whether all other options have been tried, and the patient's potential reaction if the treatment does not work.

In the area of treatment-resistant depression, the literature is supportive but not yet sufficient to recommend clinical use of DBS. *DBS for depression is not FDA approved and should only be performed in well-controlled research studies*. Because the functional neuroanatomy of depression is not nearly as well known as that for Parkinson's disease or dystonia, a great deal of caution is needed in this area. Psychiatrists should not re-create the mistakes

of the lobotomy years, where overenthusiastic adoption of an invasive technology ruined many lives and damaged the reputation of a field.

Other Brain Stimulation Treatments

Brain stimulation treatments constitute a fertile and rapidly growing field, with many additional techniques emerging almost monthly. In general, it is best to adopt an open but skeptical approach to these treatments. In other words, they might work, but rigorous RCTs are needed before adoption.

Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is a brain stimulation technique achieved through application of constant weak (typically ≤1mA) electrical current through scalp electrodes. Unlike TMS, tDCS does not elicit action potentials in cortical neurons. Instead, the constant direct current of tDCS induces subthreshold changes in membrane potential that increase or decrease the ease with which an action potential may be triggered (Leung et al. 2009). These changes in cortical excitability were first documented using motor potentials evoked with TMS. Although tDCS is currently just an investigational tool, studies have shown that it may also have therapeutic applications.

Brief History

Although the first formal use of modern tDCS has been debated, brain stimulation techniques that use similar principles have been employed for over two centuries. With the advent of the capacitor (known as a *Leyden jar*) in the 18th century, experiments gradually began to support Luigi Galvani's concept of animal electricity over Alessandro Volta's concept of bimetallic electricity or Franz Mesmer's concept of animal magnetism. Coining the term "galvanism," Galvani's precocious nephew Giovanni Aldini began exploring the effects of direct current on decapitated livestock and corpses. Shortly after his reanimation experiments, Aldini began applying galvanism to ameliorate "melancholy madness" in hospital patients. While it is likely that Aldini also employed various waveforms other than constant direct current, his macabre methodology undoubtedly contributed to the development of tDCS-like techniques. One such technique was pioneered by Guillaume-Benjamin-Amand Duchenne de Boulogne, a neurologist who used a small generator and battery to examine the effects of direct current on muscle contraction and disorders such as muscular dystrophy (George 1994). When Duchenne's historic experiments failed to reveal clinical applications for direct current stimulation, interest in the technique waned. Outside of a few studies on "electrosleep therapy" in the early 20th century, largely in Russia, tDCS was ignored until Walter Paulus and colleagues began investigating its effects on neurophysiology.

Research

There are currently no FDA-approved therapeutic uses for tDCS. Nevertheless, tDCS remains an active area of research because of the ease with which it can be applied and the flexibility derived from its various potential electrode placements. A small current source and damp sponges (electrodes) are all that are required for tDCS administration. This portable, safe, inexpensive setup is particularly alluring because it may enable

tDCS to be used in nontraditional ways, including in a patient's home or during therapeutic interventions such as cognitive behavioral therapy or rehabilitation exercises. tDCS has the capacity to alter cortical excitability and intracortical inhibition (Tremblay et al. 2013). The next step is to determine how physicians might use this form of non-invasive neuromodulation for therapeutic purposes.

Thus far, the most promising effects of tDCS have been found in rehabilitation studies. Although more randomized controlled trials are needed, there is emerging evidence that tDCS may enhance poststroke aphasia rehabilitation therapies. A few studies have begun to explore the circuitry changes induced by tDCS, but precise mechanisms remain largely unknown. There is also evidence to suggest that tDCS augments poststroke motor recovery, but these studies frequently feature small sample sizes, heterogenous outcome measures, and mixed results (Bastani and Jaberzadeh 2012). These limitations also apply to studies investigating tDCS as a treatment for conditions like pain and depression (Kalu et al. 2012). Although tDCS shows some promise for many different clinical applications, there is currently insufficient evidence in most clinical diseases.

tDCS in Major Depressive Disorders

Results of clinical trials conflict concerning the efficacy of tDCS in major depression. A 2012 systematic review and meta-analysis of four open-label trials and six RCTs, with a total of 108 subjects, found that tDCS was effective in reducing depressive symptoms (Kalu et al. 2012). However, a subsequent review of many of the same studies reached different conclusions (Berlim et al. 2013) (Table 15–2). Six RCTs, with a total of 200 subjects with major depression, found no significant difference between active and sham tDCS in terms of both response and remission of major depression. This finding contrasts with those from earlier sham-controlled trials (Boggio et al. 2008; Fregni et al. 2006; Nitsche et al. 2008). Berlim and colleagues maintain that their 2013 review focused on clinically relevant outcome measures—namely, response and remission rates—that had significantly higher statistical power than those utilized in the 2012 review by Kalu and colleagues.

Findings from the most extensive and well-conducted tDCS trial to date for depression were recently published (Brunoni et al. 2013). At a single center in Brazil, Brunoni and colleagues randomly assigned 120 depressed outpatients in a 2x2 design to sertraline or placebo and anodal left, cathodal right prefrontal tDCS or sham. The tDCS was given in 12 sessions. Patients in the combined tDCS/sertraline group had a significantly greater reduction in their depression scores compared with those in any of the other three arms. Reductions in depression scores were similar in the sertraline alone and the tDCS alone groups. The sertraline alone was not statistically significantly different from the sham group. There were only a few side effects, which included treatment-emergent mania (mostly in the combined treatment groups).

Thus, the ultimate clinical utility of tDCS as a treatment for major depression remains unclear but is promising. Larger, more representative samples are needed in future studies (Brunoni et al. 2012).

Unresolved Issues

There are a number of unresolved issues that need to be addressed before tDCS can be thoroughly evaluated as a therapeutic tool. One of the most fundamental issues with tDCS is the lack of clarity regarding the neurophysiological effects produced by each electrode. When tDCS

TABLE 15–2. Meta-analysis of active versus sham transcranial direct current stimulation (tDCS) for major depression in the review

	N				Response rates				Remission rates			
Study	**Active tDCS**	**Sham tDCS**	**Primary diagnosis**	**Treatment strategy**	**Active tDCS**	**Sham tDCS**	**Odds ratio**	***P***	**Active tDCS**	**Sham tDCS**	**Odds ratio**	***P***
Fregni et al. 2006	5	5	MDD	Monotherapy	4/5	0/5	33.000	0.046	N/A	N/A	N/A	N/A
Boggio et al. 2008	21	19	MDD	Monotherapy	8/21	2/19	5.231	0.058	5/21	0/19	13.000	0.090
Loo et al. 2010	20	20	MDD	Mixed[a]	6/20	4/20	1.714	0.468	5/20	3/20	1.889	0.433
Blumberger et al. 2012	13	11	MDD	Augmentation	1/13	1/11	0.833	0.902	1/13	1/11	0.840	0.932
Loo et al. 2012	33	31	MDD (86.5%) BD (13.5%)	Mixed[b]	4/33	4/31	0.931	0.925	1/33	1/31	0.938	0.975
Palm et al. 2012	11	11	MDD (90.1%) BD (9.9%)	Augmentation	1/11	1/11	1.000	1.000	1/11	1/11	1.000	1.000
Overall					**24/103**	**12/97**	**1.974**	**0.112**	**12/98**	**5/92**	**2.131**	**0.216**

Note. MDD=major depressive disorder; BD=bipolar disorder.
[a]Augmentation strategy in 35% and 65% of the subjects receiving active and sham tDCS, respectively; monotherapy in 65% and 35% of the subjects receiving active and sham.
[b]Augmentation strategy in 71% and 72.5% of the subjects receiving active and sham tDCS, respectively; monotherapy in 29% and 27.5% of the subjects receiving active and sham tDCS, respectively.
Source. Adapted from Berlim et al. 2013.

is applied, direct current typically flows from energy source to anode to cathode. Although most studies have found that anodal stimulation and cathodal stimulation normally increase and decrease cortical excitability, respectively, others have found circumstances under which these polarity effects may be reversed. More studies are needed to clarify how brain complexities such as neuronal morphology and network connectivity affect neuronal response to tDCS.

Another unresolved tDCS issue pertains to dose titration. Unlike TMS, which can be titrated based on MT, tDCS is not typically tailored for each individual patient. It may be the case that experimental trials fail to find significant behavioral results because the dose of tDCS used in many individuals is insufficient for the induction of durable changes in neural excitability. Once tDCS doses can be titrated, then studies can begin to explore tDCS in a more systematic way.

Moreover, there are no dose-finding studies, or even systematic safety studies, with tDCS. The current limit of 2 mA is largely based on consensus and the potential for scalp burns, but higher doses are possible and are probably safe.

In addition to acupuncture, there are several different small portable stimulation methods, like transcutaneous electrical nerve stimulation (TENS) units, that stimulate peripherally and purport to change brain function. These use biphasic, low-volt, current and selectable parameters such as pulse rate and pulse width to stimulate sensory nerves to block pain signals, and theoretically alter brain function. As a class, there are broad neuropsychiatric therapeutic claims bandied about on the Internet and in advertisements, which are not based on rigorous RCT data. Some devices in this group are designed to stimulate the earlobe, which has complex afferent fibers (including branches of the vagus nerve). Some of these devices were in production when the legislation creating the devices branch of the FDA was passed and approved, and they were "grandfathered" in, without clear evidence of efficacy.

Conclusion

The brain stimulation therapies are now an established part of the psychiatrist's toolbox, especially in treating mood disorders. This is a rapidly expanding area that holds promise for even more advances in terms of treatments for neuropsychiatric conditions.

Key Points

- The brain is fundamentally an electrochemical organ, where electrical impulses serve as the basis for information flow and then cause neurotransmitter release. Electrical stimulation of the brain can thus theoretically cause focal neuropsychopharmacological changes without the side effects of systemic medications.
- The brain stimulation therapies as a class share several common concepts and principles and can be understood by realizing which procedures produce seizures on purpose (electroconvulsive therapy [ECT], magnetic seizure therapy, focal electrically administered seizure therapy) and which do not (transcranial magnetic stimulation [TMS], vagus nerve stimulation (VNS), deep brain stimulation [DBS]).

- ECT is our most effective treatment for acute major depression.
- TMS is an exciting research tool and is U.S. Food and Drug Administration–approved for treating depression.
- Repeated daily prefrontal TMS for 4–6 weeks has acute antidepressant effects similar to those of medications or ECT, with few side effects.
- VNS is an FDA-approved treatment for epilepsy as well as treatment-resistant depression. VNS is best reserved for patients with a long history of depression (chronic) who have failed or cannot be given most other options.
- More research on the fundamental neurobiological effects of brain electrical stimulation will help these new techniques continue to be improved and evolve.
- DBS for depression is not FDA approved. A humanitarian device exemption (HDE) has been granted by the FDA for using DBS for treatment-resistant obsessive-compulsive disorder.

Recommended Readings

General

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Useful Web Sites

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PART IV

Anxiety Disorders and Obsessive-Compulsive and Related Disorders

Franklin R. Schneier, M.D.
Barbara Milrod, M.D.

Anxiety disorders are the most common mental disorders among adults in the United States, with a lifetime prevalence rate of 29% and a 12-month prevalence rate of 18% (Kessler et al. 2005a, 2005b). Most persons with anxiety disorders experience significant impairment in role functioning (Kessler et al. 2005b), and costs associated with anxiety disorders have been estimated at more than $42 billion per year, including lost productivity, excess mortality, and treatment costs (Greenberg et al. 1999). While increasing numbers of people with anxiety disorders are seeking treatment (Olfson et al. 2004), first treatment contact is still typically delayed more than 10 years after onset of the disorder (Wang et al. 2005), indicating a continued need for better community education and access to treatment.

The anxiety disorders have undergone a sea change in DSM-5. While anxiety disorders historically have been classified together based on the prominence of the symptom of anxiety among them, researchers and clinicians have increasingly highlighted distinctions among the disorders within this category. In DSM-5, obsessive-compulsive disorder (OCD) is grouped apart from the anxiety disorders and is instead categorized with four other disorders that share obsessions or compulsive behaviors: trichotillomania (or hair-pulling disorder, previously described as an impulse-control disorder), body dysmorphic disorder (BDD; previously described as a somatoform disorder), excoriation disorder (or skin-picking disorder, new to DSM-5), and hoarding disorder (previously subsumed under OCD). Posttraumatic stress disorder and acute stress disorder have been relocated from the anxiety disorders diagnostic class to a new class "Trauma- and Stressor-Related Disorders" (see Chapters 27, "Post-

traumatic Stress Disorder," and 28, "Acute Stress Disorder," in Part V of this volume), based on the required diagnostic features of having an abnormal response to a stressor or traumatic event. Panic disorder, generalized anxiety disorder (GAD), and phobic disorders (i.e., social anxiety disorder, agoraphobia, and specific phobia) remain as core diagnoses within the anxiety disorders class. New additions to this category include separation anxiety disorder and selective mutism, previously categorized within "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence."

The authors of chapters in Part IV review empirical support for the efficacy and effectiveness of treatments for anxiety disorders and obsessive-compulsive and related disorders, a literature that has grown tremendously since the early 1980s. In particular, numerous studies have established the efficacy of specific forms of cognitive-behavioral therapy (CBT) for specific disorders within these categories, and the efficacy of selective serotonin reuptake inhibitors (SSRIs) for panic disorder, social anxiety disorder, OCD, GAD, and possibly BDD. In recent years, the treatment research literature has largely focused on refinement of these established treatments and exploration of alternative novel approaches. A small but growing literature addresses alternative psychotherapies (e.g. disorder-specific brief psychodynamic psychotherapies, CBT approaches incorporating mindfulness) and alternative classes of medications, combined approaches, treatment of treatment-refractory conditions, and the treatment of comorbid syndromes. There remains a need for research of novel treatments, given that each of these categories of illness is characterized by limited response and remission rates to first-line treatments.

In Chapter 16, "Panic Disorder," Murray Stein and colleagues review treatments for panic disorder. They note that SSRIs are established as the first-line pharmacotherapy and that benzodiazepines also have a role in treatment of many of these patients. Effective CBT approaches to panic incorporate psychoeducation, identification and modification of panic-related cognitions, exposure to feared sensations and situations, and relapse prevention techniques. The authors also review a novel evidence-based dynamic therapy for panic disorder.

Separation anxiety disorder treatment is reviewed by Jill Cyranowski and Barbara Milrod in Chapter 17, "Separation Anxiety Disorder." Until recently, separation anxiety disorder was believed to occur almost exclusively in children, as reflected in its classification within DSM-IV as a disorder of childhood onset. That explains in part why there has been virtually no study of treatment of this condition in adults, despite adult prevalence rates of at least 2%–3% reported in community samples. In children, anxiety disorders are relatively less differentiated from one another, but findings from studies of children with separation anxiety disorder, social anxiety disorder, and/or GAD have supported the efficacy of CBT and SSRI medications.

Social anxiety disorder is reviewed by Franklin Schneier and colleagues in Chapter 18, "Social Anxiety Disorder (Social Phobia)." The authors describe established CBTs for social anxiety disorder that utilize cognitive restructuring and exposure to feared situations through role-playing and homework assignments. SSRIs are first-line pharmacotherapies, with serotonin-norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, and monoamine oxidase inhibitors among other established options.

In Chapter 19, "Generalized Anxiety Disorder," Michelle Newman and colleagues discuss CBT that incorporates identifying anxiety triggers with the use of cognitive retraining, desensitization, and development of anxiety management skills for treatment of GAD. Variants of CBT incorporate emotion processing and interpersonal techniques. Psychodynamic therapy studies are reviewed, as is the evidence for efficacy of SSRIs, benzodiazepines, and alternative classes of medications.

Specific phobias, reviewed by Joshua Lipsitz in Chapter 20, "Specific Phobia," are the prototypical disorders for which exposure-based treatments have been shown highly effective. The author reviews the development and refinement of these techniques, along with preliminary findings for alternative therapies and medication.

OCD treatments are reviewed by John Greist and James Jefferson in Chapter 21, "Obsessive-Compulsive Disorder." Exposure in vivo and ritual prevention constitute the well-established first-line treatment for OCD, with efficacy superior to that of medications in comparative studies. SSRIs and clomipramine remain the mainstays of pharmacotherapy for OCD, although their limited efficacy has prompted a search for augmenting agents. Of these, the atypical antipsychotics have strongest evidence for efficacy at present.

Katharine Phillips, in Chapter 22, "Body Dysmorphic Disorder," reviews treatments for BDD. Although treatments for BDD have been far less studied than those for OCD, the approaches to these disorders have some commonalities. SSRIs are the preferred medication treatment for BDD, based on two controlled trials and multiple open-label studies. Preliminary studies of CBT suggest efficacy for approaches that combine standard exposure and response prevention with cognitive retraining and perceptual retraining techniques more specific to BDD.

In Chapter 23, "Hoarding Disorder, Trichotillomania (Hair-Pulling Disorder), and Excoriation (Skin-Picking) Disorder," Nastassja Koen and Dan Stein review treatments for hoarding disorder, trichotillomania (hair-pulling disorder), and excoriation (skin-picking) disorder. They note that treatments of these relatively new disorders have been less developed than those for OCD or most anxiety disorders. Among medication approaches, there is some evidence of utility of SSRIs for all these disorders, and there is early evidence for the use of *N*-acetyl cysteine in trichotillomania and excoriation disorder. CBT treatments, such as habit reversal therapy, have also been adapted for each of these disorders and have preliminary evidence for efficacy.

These chapters recognize what is now a wealth of data supporting efficacious treatments for specific anxiety disorders and OCD, and growing evidence for treatments for separation anxiety disorder and for BDD and the other obsessive-compulsive and related disorders. In addition to the best-studied modalities of CBT and SSRIs, research and clinical experience suggest that psychodynamic therapies and a variety of lesser-studied medications may also be useful for specific disorders. New directions in the field, many of which could not be discussed here due to space limitations, include preliminary efforts to harness new findings from neuroscience to develop treatments, such as cognitive enhancers of CBT, modulators of glutamate, and somatic therapies such as transcranial magnetic stimulation. Much also remains to be learned about optimizing existing treatments for individual patients, including development of better support for personalization of selection of initial treatment, augmentation of partial re-

sponses, and maintenance of responses over the long term.

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CHAPTER 16

Panic Disorder

Murray B. Stein, M.D., M.P.H.
Calvin T. Yang, M.D., Ph.D.
Laura Campbell-Sills, Ph.D.

In this chapter we review pharmacological and psychological treatments for panic disorder. The recommendations stem from a combination of practice guidelines (American Psychiatric Association 2009) and review of the literature. We focus on interventions that have solid empirical support in the form of at least one well-designed randomized controlled trial (RCT). For pharmacological treatments, we avoid providing specific dosing recommendations for particular drugs, as this information may be obtained from other sources that are frequently updated (e.g., manufacturers' Web sites). We do not discuss the treatment of special populations (e.g., older adults, children, pregnant women) because of space limitations.

Panic disorder is characterized by recurrent panic attacks that occur, at least early in the illness, unexpectedly and are followed by persistent concern, worry, or change in behavior in relation to the attacks. In many cases, the change in behavior involves avoidance of places or activities the individual believes will be difficult to escape from if panic attacks were to occur. DSM-5 diagnostic criteria for panic disorder are presented in Box 16–1.

Box 16–1. DSM-5 Diagnostic Criteria for Panic Disorder

300.01 (F41.0)

A. Recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (or more) of the following symptoms occur:

Note: The abrupt surge can occur from a calm state or an anxious state.

1. Palpitations, pounding heart, or accelerated heart rate.
2. Sweating.
3. Trembling or shaking.
4. Sensations of shortness of breath or smothering.
5. Feelings of choking.
6. Chest pain or discomfort.
7. Nausea or abdominal distress.
8. Feeling dizzy, unsteady, light-headed, or faint.
9. Chills or heat sensations.
10. Paresthesias (numbness or tingling sensations).
11. Derealization (feelings of unreality) or depersonalization (being detached from oneself).
12. Fear of losing control or "going crazy."
13. Fear of dying.

Note: Culture-specific symptoms (e.g., tinnitus, neck soreness, headache, uncontrollable screaming or crying) may be seen. Such symptoms should not count as one of the four required symptoms.

B. At least one of the attacks has been followed by 1 month (or more) of one or both of the following:
   1. Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, "going crazy").
   2. A significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).

C. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).

D. The disturbance is not better explained by another mental disorder (e.g., the panic attacks do not occur only in response to feared social situations, as in social anxiety disorder; in response to circumscribed phobic objects or situations, as in specific phobia; in response to obsessions, as in obsessive-compulsive disorder; in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder).

Accepted treatments of panic disorder include pharmacological treatment, psychological treatment, or a combination of the two. Many factors play a role in selection of a treatment modality, including patient preference, availability of treatment options, and prior response to treatments.

Pharmacological Treatments

Donald Klein's (1964) observation that the tricyclic antidepressant (TCA) imipramine blocked panic attacks in hospitalized patients ushered in the era of psychopharmacological treatments for panic disorder. It has subsequently been shown that several classes of antidepressants are effective in the treatment of panic disorder, as are certain benzodiazepines.

The pharmacological treatment of panic disorder is aimed not only at reducing or eliminating panic attacks but also at reducing avoidance behavior, anticipatory anxiety, and comorbid conditions such as major depressive disorder or other anxiety disorders. Although the neurobiology of panic disorder is far from being

completely understood, incremental advances in functional neuroimaging—such as positron emission tomography studies with serotonin receptor subtype–specific ligands (Neumeister et al. 2004) and magnetic resonance spectroscopy studies measuring γ-aminobutyric acid (GABA) levels in the central nervous system (Goddard et al. 2004)—are consonant with clinical observations that manipulations in brain serotonergic and/or GABAergic systems underlie the effects of most available panic disorder pharmacotherapies.

Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), TCAs, and benzodiazepines have demonstrated efficacy in panic disorder. Selecting an initial pharmacological intervention often involves consideration of patient preference, medical history, past treatments, drug interactions, and side-effect profiles. SSRIs and SNRIs are typically the preferred first-line treatments because of their ability to treat comorbid mood and anxiety disorders and their more tolerable side-effect profile relative to TCAs (American Psychiatric Association 2009).

Patients with panic disorder are often particularly sensitive to perceived side effects, so starting at a very low dose of an antidepressant for several days before titrating upward is generally recommended. Augmentation with a low dose of a benzodiazepine can allow for increased rate of antidepressant titration. Antidepressants can take 3–4 weeks to exhibit their therapeutic effect in panic disorder, whereas benzodiazepines are immediately effective. It should be noted that most of the pharmacological RCTs in panic disorder have been of relatively short duration (e.g., 12 weeks), making it difficult to extrapolate to make recommendations about optimal duration of treatment. If, after an adequate trial, no response is achieved, the recommendation is to switch to a different drug in another class. In the case of a partial response, the clinician can consider increasing the dose, augmenting with another agent such as benzodiazepines, or augmenting with an empirically supported psychosocial intervention. Once the patient has satisfactory response, the recommendation is often made to continue medication management for at least 1 year. If the patient has been stable and discontinuation of medications is desired, a slow taper over several weeks to months is recommended. A slow taper is necessary to reduce risk of relapse in which case the dose can be titrated back to the previous dose. There are some data supporting the utility of half-dose maintenance for 1 year during an SSRI taper (Mavissakalian and Perel 2001).

Antidepressants

Selective Serotonin Reuptake Inhibitors

SSRIs have been well established as a treatment for panic disorder. Paroxetine was the first SSRI approved by the U.S. Food and Drug Administration (FDA) for the treatment of panic disorder, and there are numerous RCTs demonstrating its safety and utility (e.g., Ballenger et al. 1998). Sertraline, another SSRI approved by the FDA for the treatment of panic disorder, also has a large body of evidence demonstrating its safety and utility (Pohl et al. 1998). Other SSRIs, including fluoxetine (FDA approved) (Michelson et al. 2001), fluvoxamine (Asnis et al. 2001), and citalopram (Wade et al. 1997) and its enantiomer escitalopram (Stahl et al. 2003), have one or more published RCTs showing their efficacy and safety in the treatment of panic disorder.

It is our opinion that all drugs in this class are equally effective in the treatment of panic disorder. There have not been

RCTs demonstrating superiority of one SSRI over another. Currently, fluoxetine, paroxetine, and sertraline have FDA indications for use in treatment of panic disorder. Because of decreased likelihood of drug-drug interactions and decreased side effect burden, escitalopram, citalopram, and sertraline may be preferred relative to the other SSRIs. For patients with a history of SSRI treatment, the particular SSRI that proved beneficial in the past would usually be the one to start with. Specific side-effect profiles could be taken into account, and recent FDA guidelines, such as precautions regarding cardiac QT interval prolongation in citalopram, are important to consider.

Serotonin-Norepinephrine Reuptake Inhibitors

Of the SNRIs, venlafaxine has been found to be effective in treating panic disorder (Bradwejn et al. 2005) and may have similar or better efficacy than paroxetine (Pollack et al. 2007). Venlafaxine has also recently obtained FDA approval for this indication. Although duloxetine and milnacipram also have dual serotonin and norepinephrine action, there have not been any RCTs demonstrating their efficacy in panic disorder.

Tricyclic Antidepressants

TCAs such as imipramine and heterocyclic antidepressants (e.g., desipramine, clomipramine) are also efficacious in the treatment of panic disorder (Modigh et al. 1992). Considerations for using a TCA would include contraindications such as narrow angle glaucoma and benign prostatic hypertrophy, potential for cardiac arrhythmias, increased risk of falls in elderly due to orthostasis and sedation, and toxicity in overdose. A baseline electrocardiogram is required prior to starting a TCA because of the risk of exacerbating a cardiac conduction defect. Within the class of TCAs, desipramine or nortriptyline may be preferred because of less sedation, fewer anticholinergic side effects, and decreased risk of orthostatic hypotension.

Benzodiazepines

Benzodiazepines, including (but not limited to) alprazolam, clonazepam, diazepam, and lorazepam, have been well established as an effective treatment for panic disorder. Although SSRIs and SNRIs are considered first-line treatments, in severe cases or when first-line treatments fail, benzodiazepines can be quite effective both as monotherapy and for augmentation. Relief of symptoms is quick as opposed to antidepressants, which can take 4–6 weeks to achieve some effect and often longer for full effect. Nevertheless, antidepressants have proven efficacy in treatment of comorbid depression as well as other anxiety disorders. It is recommended to use benzodiazepines judiciously because of the potential for abuse in high-risk patients and the possibility of tolerance. (For example, do not prescribe under most circumstances to persons with known substance abuse histories; monitor risk–benefit ratios for use on a regular basis throughout treatment.)

Benzodiazepine Monotherapy

Most RCTs of benzodiazepines have involved the high-potency agents alprazolam or clonazepam. Both of these medications are safe and effective in the treatment of panic disorder (Pecknold et al. 1994), although concerns have been raised about the toxicity of alprazolam in the case of overdose. Alprazolam, which has a more rapid onset and a shorter duration of action than clonazepam, may

also be more difficult to taper, and withdrawal symptoms may mimic panic symptoms and thereby complicate discontinuation or dosage reduction. There is no reason to believe that these two benzodiazepines are unique in their antipanic efficacy. Although concern about tolerance to the effects of benzodiazepines is often voiced as an issue that limits their use, tolerance to long-term use is not common, even though some tolerance is common during initiation of benzodiazepines (Worthington et al. 1998).

Adjunctive Use of Benzodiazepines

Adjunctive use of benzodiazepines can accelerate the speed of response to pharmacotherapy, compared with SSRIs alone (Smith at al. 1998). By the time some patients with panic disorder seek treatment, they may be at the point where their symptoms are compromising their ability to function (e.g., in the workplace) and waiting 3–4 weeks for an SSRI to work is not an acceptable option. In such cases, it is possible to administer an adjunctive benzodiazepine for the first few weeks (either scheduled for prevention or as needed [PRN] for breakthrough symptoms) with the plan to taper once the SSRI has achieved some measure of efficacy.

Other Pharmacotherapeutic Agents

Other pharmacotherapies that currently have limited evidence or no evidence for effectiveness include mirtazapine, anticonvulsants, propranolol, pindolol, D-cycloserine, buspirone, and second-generation antipsychotics. Additional studies are required to determine if these treatments may be beneficial.

Psychological Treatments

Cognitive-behavioral therapy (CBT) has been rigorously tested in multiple RCTs and can be recommended with confidence as a first-line treatment for panic disorder (American Psychiatric Association 2009). Because CBT has the most extensive evidence base, we devote the majority of this section to describing its major components and reviewing research related to optimizing its effects and utilization. Another psychological treatment, panic-focused psychodynamic psychotherapy (PFPP), which has one published RCT supporting its efficacy and a partial replication in press (Beutel et al. 2013), will also be described. A number of other psychological treatments for panic disorder either have not shown superiority to credible placebos or have proven inferior to other treatments such as CBT.

Cognitive-Behavioral Therapy

An extensive literature that includes rigorously executed RCTs (e.g., Barlow et al. 2000) and meta-analyses (e.g., Hofmann and Smits 2008) supports the efficacy of CBT for panic disorder. CBT is effective when delivered on an individual basis (e.g., Barlow et al. 2000) or in a group format (e.g., Marchand et al. 2009). RCTs have further shown that CBT improves outcomes for patients treated in primary care (Craske et al. 2011), indicating that its benefits are transportable to clinical practice (vs. research) settings. Though several studies report good long-term outcomes with CBT (e.g., at 21- to 24-month

follow-up; Marchand et al. 2009), strong conclusions about long-term efficacy are hindered by methodological problems (Nadiga et al. 2003).

Although there is strong evidence for the efficacy of CBT for panic disorder, there are many patients whose symptoms do not respond fully to CBT. For example, in the largest trial of CBT for panic disorder to date, only about half of the patients assigned to receive CBT were considered "responders" following acute treatment (Barlow et al. 2000). Therefore, recent research has focused on evaluation of strategies for optimizing efficacy of CBT and investigation of predictors and moderators of treatment outcome. In addition, the relative underutilization of CBT has prompted investigation of formats that could improve dissemination efforts (e.g., brief protocols; Internet delivery; "trans-diagnostic" treatments).

Theoretical Basis of CBT

Cognitive-behavioral conceptualizations of panic disorder are based on behavioral theories of fear conditioning (Bouton et al. 2001) and cognitive theories that highlight the role of anxious thinking (Clark 1986). More behaviorally oriented CBT models hypothesize that anxiety and panic have become conditioned reactions to certain *interoceptive* cues (i.e., internal states such as change in heart rate) and *situational* cues (i.e., external situations such as enclosed spaces). When interoceptive or situational cues have been associated with panic on multiple occasions, they come to reliably elicit the panic response in a classical conditioning fashion (Bouton et al. 2001). Treatment therefore must address the learned associations between these cues and panic responses.

Most CBT models also acknowledge a role for anxiety-escalating cognitions in panic disorder. Clark (1986) notably referred to this type of thinking as "catastrophic misinterpretations of bodily sensations." Common misinterpretations of sensations associated with panic attacks include the beliefs that one is having a heart attack, fainting, "going crazy," or even dying. Individuals with panic disorder also may be preoccupied with anxious thoughts about nonphysical consequences of panic symptoms (e.g., social embarrassment). Consequently, correcting anxious cognitions about physical sensations is considered an integral part of treatment for panic disorder.

Components of CBT

Although specific CBT protocols vary somewhat in their elements and emphasis, they share several core components, which are discussed below.

Psychoeducation. Psychoeducation serves several important purposes in CBT, including facilitating a strong therapeutic alliance, providing the patient with a sense of hope and self-efficacy, and enhancing motivation. Many patients enter therapy with beliefs that panic symptoms are dangerous and may lead to disastrous outcomes such as fainting, having a heart attack, "going crazy," or dying. The therapist provides corrective information centered on the idea that the symptoms of panic disorder result from a harmless (albeit uncomfortable) misfiring of the body's "fight-or-flight" system. This information alone may help some patients reinterpret their symptoms in a less anxiety-provoking manner, leading to less severe and less frequent panic attacks. Psychoeducation further addresses the role of avoidance in maintaining fear. Patients learn that avoidance sends a message of danger and prevents the natural process of habituation from occurring. An understanding of the negative effects of avoidance may enhance motivation for exposure.

Cognitive restructuring. Patients with panic disorder endorse a wide range of anxious cognitions focused on physical catastrophes, loss of control, negative social evaluation, and inability to maintain role functioning. Cognitive restructuring helps patients learn to identify thoughts that contribute to panic episodes, and to recognize common errors in thinking that frequently accompany fear and anxiety (e.g., overestimation of the likelihood of negative events and underestimation of one's ability to cope with feared outcomes). Patients then generate alternative beliefs that focus on consideration of the objective evidence. Patients typically need to repeat cognitive restructuring exercises many times before realistic, adaptive thinking can compete with the previously held anxious beliefs.

Exposure. Exposure is one of the most powerful aspects of CBT, and also one of the most challenging. Patients therefore must be well prepared and adequately supported through this process.

Interoceptive exposure is a central component of many CBT protocols, because it targets the "core" of panic disorder—the fear of physical sensations. Interoceptive exposure entails deliberately eliciting physical symptoms in a repeated fashion in order to break the association between the symptoms and the fear reaction. The level of fear of various physical symptoms is first assessed through a series of exercises designed to bring on different sensations (e.g., breathing through a straw for breathlessness, spinning in a chair for dizziness). The therapist assigns repeated practice of each feared exercise until the patient can experience the symptoms without significant fear.

Most patients with panic disorder also develop a pattern of fear and avoidance of specific situations in which having a panic attack would be particularly distressing (agoraphobia). Patients are encouraged to confront these situations during *situational (or "in vivo") exposure*. Patients develop a "fear and avoidance hierarchy" that lists situations by their level of difficulty. Through the course of CBT, they gradually confront each situation repeatedly until their level of fear subsides.

Relapse prevention. The final sessions of CBT generally focus on consolidating skills and increasing independence. Therapists remind patients that their "old habits" of anxious thinking and behavior are still quite strong and that continued practice of CBT skills is necessary in order to maintain and extend improvement.

Combining CBT and Pharmacotherapy

Recent studies have demonstrated some short-term incremental benefits of combination treatment over monotherapy with CBT (Barlow et al. 2000; van Apeldoorn et al. 2010). However, many questions remain regarding the cost-benefit profiles of combination treatment versus CBT alone. In particular, there is some empirical support for concerns that concomitant pharmacotherapy may attenuate some of the longer-term benefits of CBT (Barlow et al. 2000; Marks et al. 1993; Watanabe et al. 2007). Cost-effectiveness is also an important consideration, and available analyses suggest that CBT is more cost-effective in the long term than combination treatment (McHugh et al. 2007).

The largest-scale study that has addressed this topic compared the acute and long-term effects of CBT, imipramine, CBT plus imipramine, placebo, and CBT plus placebo (Barlow et al. 2000). Individuals who were classified as responders to 11 sessions of acute treatment

received 6 months of maintenance treatment (one session monthly of whichever treatment they had received in the acute phase). Results showed that all four active treatment conditions were superior to pill placebo. There were no significant differences in the effects of CBT alone and imipramine alone in the acute or maintenance phases of the study. More improvement was seen in the CBT plus imipramine group than in the CBT group on some posttreatment measures; however, the CBT plus imipramine combination was never superior to CBT plus placebo. This suggested that the short-term benefit of adding imipramine to CBT approximated a placebo effect. By the end of the 6-month maintenance phase, the combination of CBT and imipramine had produced the best response (superior to CBT alone and CBT plus placebo); however, CBT plus imipramine also was associated with the highest relapse rate 6 months after treatment withdrawal. At best, combination treatment appeared to produce a superior short-term response; however, this advantage appeared to have been at the expense of greater relapse following withdrawal of CBT (Barlow et al. 2000).

A more recent study compared the effects of CBT plus an SSRI to the effects of each treatment administered alone (van Apeldoorn et al. 2010). The period of active treatment was 1 year, after which all treatments were discontinued. CBT plus SSRI was superior to CBT alone on several outcome measures after 9 months of treatment; however, there were no differences among the treatment conditions immediately after treatment discontinuation or at 6- and 12-month follow-ups.

With respect to combining CBT and benzodiazepines, the largest available RCT showed that adding alprazolam to exposure marginally enhanced gains during acute treatment. However, relapse rates were higher among patients who received exposure plus alprazolam after treatment withdrawal than among patients who received exposure plus placebo (Marks et al. 1993).

Consistent with the results of the studies described above, meta-analyses have found that CBT plus pharmacotherapy is superior to monotherapy during the active phase of treatment (Furukawa et al. 2006; Hofmann et al. 2009). However, it has also been concluded that combined treatment produces more dropouts than CBT alone and that its effects are equivalent to those of monotherapy with CBT after active treatment has been withdrawn (Furukawa et al. 2006). When cost-effectiveness analyses favoring CBT alone over combination treatment are considered (McHugh et al. 2007), the argument for combination treatment as a first treatment step for panic disorder is less compelling. These observations are complicated by a range of approaches to pharmacological discontinuation in these studies.

Use of CBT to Aid in Benzodiazepine Discontinuation

Many patients who take medications for panic disorder wish to terminate pharmacotherapy at some point. Reasons for medication discontinuation may be practical (e.g., cost), medical (e.g., side effects), or personal (e.g., dislike of being "dependent" on medication, desire to become pregnant).

As noted earlier in this chapter, benzodiazepines are effective in treating the symptoms of panic disorder but are notoriously difficult for some patients to discontinue because of recurrence of panic or withdrawal symptoms. The characteristic benzodiazepine withdrawal syndrome includes nervousness, irritability, sleep disturbance, dizziness, and tremor.

Several of these symptoms are precisely those that can trigger panic attacks. Several RCTs have shown that CBT is more beneficial than supportive medical management in helping patients to discontinue benzodiazepines (Otto et al. 1993; Spiegel et al. 1994). A recent study also demonstrated that CBT was superior to a relaxation-based intervention in producing successful discontinuation of benzodiazepine use (Otto et al. 2010), indicating that the benefits of CBT are specific to the intervention rather than being related to nonspecific factors such as therapist attention. The majority of patients who receive CBT while completing a benzodiazepine taper are successful in discontinuing medication use by the end of acute treatment. A long-term follow-up study of patients from two benzodiazepine discontinuation studies demonstrated that approximately 75% of patients who received CBT did not require any further treatment for panic disorder during the subsequent 2–5 years (Bruce et al. 1999). By contrast, 70% of patients who received the same taper program with supportive medical management required further treatment for panic disorder during this interval.

Use of CBT With Medication Nonresponders

There is only one published RCT of CBT for panic disorder in medication nonresponders. This study utilized a three-phase treatment design; patients who reached the third phase were nonresponders to sertraline or escitalopram who were randomly assigned to receive either CBT or medication optimization (adding clonazepam to the SSRI). Conclusions from this study are limited by the small sample size in the third phase (n=19). CBT did not differ from medication optimization in producing additional clinical improvement, and effect sizes for both "next-step" strategies were small. More large-scale, well-designed research is needed on this important topic.

Panic-Focused Psychodynamic Psychotherapy

Psychodynamic theories of panic disorder hypothesize that panic symptoms carry psychological meaning, and that working to uncover these unconscious meanings will lead to symptom relief and improved functioning (Milrod et al. 2007). Panic-focused psychodynamic psychotherapy (PFPP) is a brief, manualized psychotherapy based on this theory. It is designed to be delivered in twice-weekly sessions over a period of 12 weeks. The focus of PFPP is the exploration of the circumstances, emotions, and personal meanings that accompany panic episodes. The transference is viewed as one of the therapeutic agents promoting change, and direct exposure to agoraphobic situations and other panic cues is not required.

The aim in the first phase of PFPP is to relieve panic symptoms and decrease agoraphobic avoidance. It focuses on an exploration of the circumstances and feelings surrounding the onset of panic attacks, as well as an exploration of the personal meanings of panic symptoms and the personal feelings that characterize panic episodes. The therapist helps the patient recognize how certain psychodynamic conflicts (e.g., separation versus autonomy; anger and its expression) relate to panic attacks and agoraphobia.

In the second phase of PFPP, the aim is to reduce vulnerability to panic through understanding and altering of core, unconscious conflicts that are hypothesized to cause the symptoms of panic disorder.

This is accomplished by addressing transference issues and by "working through" or demonstrating that the patient's core conflicts appear across many areas of life. It is hypothesized that this phase will result in better interpersonal functioning; less conflict and anxiety around separation, anger, and sexuality; and reduced vulnerability to panic.

In the third and final phase of PFPP, termination, the patient is allowed to re-experience core conflicts related to separation/autonomy and anger in the context of the therapeutic relationship. Although this phase may lead to a temporary recurrence of panic disorder symptoms, it ultimately strengthens the patient's ability to handle autonomy.

One small RCT (N=49) demonstrated that PFPP was superior to a credible comparison condition (applied relaxation) (Milrod et al. 2007). Results showed that patients receiving PFPP achieved significantly greater reductions in panic severity, were more likely to be classified as treatment responders based on standard definitions of "response" (Barlow et al. 2000), and had more improved psychosocial functioning at posttreatment compared with patients who received applied relaxation.

Predictors and Moderators of Psychological Treatment Outcome

Understanding the predictors of response to empirically supported psychological treatments for panic disorder may aid in treatment selection and in long-term efforts to improve outcomes for patients with panic disorder. Greater overall severity of panic disorder does not appear to compromise response to CBT. In fact, one large study found that patients with more severe panic symptoms responded more robustly to CBT (Aaronson et al. 2008). However, some work suggests that earlier onset of panic disorder and more severe agoraphobia are associated with poorer response to CBT (Dow et al. 2007a, 2007b). This issue requires further study.

Research on effects of co-occurring mental disorders has revealed few substantial impacts of comorbidity on treatment outcome. A recent meta-analysis concluded that overall level of psychiatric comorbidity does not compromise outcomes of psychological treatment for panic disorder (with CBT representing the most frequently studied psychological treatment) (Olatunji et al. 2010). In fact, greater overall comorbidity was associated with larger treatment effects. With regard to specific diagnoses, research suggests that co-occurring anxiety and unipolar mood disorders do not decrease the efficacy of CBT for panic disorder (Allen et al. 2010; Emmrich et al. 2012; Rathgeb-Fuetsch et al. 2011). However, there is preliminary evidence that the presence of co-occurring personality disorders (in particular Cluster A and Cluster C disorders) and adult separation anxiety predict poorer outcomes of CBT for panic disorder (Aaronson et al. 2008; Telch et al. 2011). In contrast, patients with Cluster C disorders were found to benefit more from PFPP than patients without this comorbidity (Milrod et al. 2007).

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CHAPTER 17

Separation Anxiety Disorder

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Diagnosis

Until the advent of DSM-5, separation anxiety disorder (SAD) was identified as a childhood anxiety disorder. The authors of the DSM-IV-TR guidebook (First et al. 2004) explicitly noted that "only rarely is it appropriate to make this diagnosis in adults…" (p. 390) but observed that many adults with other anxiety disorders have a history of childhood SAD. Nevertheless, the National Comorbidity Survey Replication (NCS-R), in assessing for SAD in adults, revealed lifetime prevalence rates of 4.1% for childhood SAD and 6.6% for adult SAD in the community (Shear et al. 2006). SAD prevalence rates are estimated to be substantially higher across both child and adult psychiatric clinic samples (Pini et al. 2010).

As defined in DSM-5, symptoms of SAD include excessive distress when facing or anticipating separation from home or attachment figures, as well as persistent worries about permanently losing or being abandoned by attachments, or of potential harm that may befall them during separations (e.g., the person falling ill, getting into an accident, dying) (Box 17–1). Individuals with SAD may be afraid to be alone or without an attachment figure close at hand, and may avoid leaving home, sleeping in bed alone, or sleeping away from home because of separation fears. For some, SAD may be accompanied by repeated nightmares regarding separation fears. Physical symptoms and somatic complaints are commonly associated with separation concerns and may include headaches, stomachaches, nausea, vomiting, or panic-like symptoms of autonomic hyperarousal. Among children with SAD, school refusal is common.

Box 17–1. DSM-5 Diagnostic Criteria for Separation Anxiety Disorder

309.21 (F93.0)

A. Developmentally inappropriate and excessive fear or anxiety concerning separation from those to whom the individual is attached, as evidenced by at least three of the following:
   1. Recurrent excessive distress when anticipating or experiencing separation from home or from major attachment figures.
   2. Persistent and excessive worry about losing major attachment figures or about possible harm to them, such as illness, injury, disasters, or death.
   3. Persistent and excessive worry about experiencing an untoward event (e.g., getting lost, being kidnapped, having an accident, becoming ill) that causes separation from a major attachment figure.
   4. Persistent reluctance or refusal to go out, away from home, to school, to work, or elsewhere because of fear of separation.
   5. Persistent and excessive fear of or reluctance about being alone or without major attachment figures at home or in other settings.
   6. Persistent reluctance or refusal to sleep away from home or to go to sleep without being near a major attachment figure.
   7. Repeated nightmares involving the theme of separation.
   8. Repeated complaints of physical symptoms (e.g., headaches, stomachaches, nausea, vomiting) when separation from major attachment figures occurs or is anticipated.

B. The fear, anxiety, or avoidance is persistent, lasting at least 4 weeks in children and adolescents and typically 6 months or more in adults.

C. The disturbance causes clinically significant distress or impairment in social, academic, occupational, or other important areas of functioning.

D. The disturbance is not better explained by another mental disorder, such as refusing to leave home because of excessive resistance to change in autism spectrum disorder; delusions or hallucinations concerning separation in psychotic disorders; refusal to go outside without a trusted companion in agoraphobia; worries about ill health or other harm befalling significant others in generalized anxiety disorder; or concerns about having an illness in illness anxiety disorder.

Indications of distress or protest on separation from one's mother or primary attachment figure are viewed as the developmental norm during early childhood. Bowlby postulated that patterns of separation distress observed among mammalian young represent an evolutionarily adaptive mechanism designed to promote survival of defenseless offspring by maintaining close proximity to adult caregivers (Bowlby 1969). Such early infant-caregiver interactions are thought to foster development of mental schemas that facilitate social bonding, development of secure attachment relationships, and subsequent use of social relationships to regulate stress reactivity later in life.

Epidemiology

SAD is common in both children and adults (Shear et al. 2006). Average age at first onset of childhood SAD is estimated to be 7–9 years—with onset occurring at a younger age than typically seen for other childhood anxiety disorders, such as generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and social anxiety disorder (Bacow et al. 2009). Higher rates of childhood SAD have been observed in girls, with some data indicating that girls may be twice as likely as boys to develop SAD (Shear et al. 2006).

SAD may persist or recur in adulthood among individuals with a history of childhood SAD, and for some individuals, SAD may have its first onset in adulthood. In DSM-5, the SAD criteria are the same for adults and children/adolescents, with use of developmentally appropriate symptom anchors. NCS-R data indicated that one-third of individuals meeting lifetime criteria for childhood SAD also met criteria for adult SAD, indicating that many individuals who experience SAD during childhood also experience persistent or recurrent SAD as adults. However, in a majority of lifetime adult SAD cases (77.5%), respondents reported first SAD onset in adulthood. Average onset of adult SAD was in the late teens or early 20s, with 80% of respondents reporting first SAD onset prior to age 30. Females predominated among those diagnosed with child and/or adult SAD, although the female:male ratio was greater among those with childhood SAD (2.2 vs. 1.4 in adults) (Shear et al. 2006).

It is noteworthy that most cases of SAD appear to go undetected or undertreated. NCS-R data indicate that only 21.8% of individuals with symptoms meeting criteria for childhood SAD reported receiving treatment during childhood, and of those who received childhood treatment, only 24.3% reported that SAD was a treatment focus. By comparison, 74.7% of those with symptoms meeting adult SAD had received treatment for emotional problems; yet again for most (nearly 70%), adult treatment focused on a comorbid condition rather than on SAD (Shear et al. 2006).

Course and Comorbidity

As compared with community-based estimates (Shear et al. 2006), higher rates of SAD are reported in clinic-based samples (Cyranowski et al. 2002). Pini et al. (2012) observed that 43% of 454 adult psychiatric outpatients with primary mood and/or anxiety disorders had symptoms that met the criteria for adult SAD. In another psychiatric clinic sample of anxious (non-OCD) pediatric patients, Hammerness et al. (2008) reported that SAD accounted for 49% of admissions. SAD is associated with high levels of disability (Busch et al. 2012) and comorbidity with other anxiety and mood disorders (Cyranowski et al. 2002; Franco et al. 2007; Shear et al. 2006). In one study, 79% of children diagnosed with SAD had symptoms that met the criteria for at least one other disorder, and 54% had symptoms that met the criteria for two or more comorbidities (Kendall et al. 2001).

Given the relatively early age at onset for pediatric SAD and the high rates of comorbidity that accompany the disorder, many have hypothesized that childhood SAD may represent a potent precursor to, or risk factor for, development of other anxiety and mood disorders. Retrospective studies suggest elevated reports of childhood SAD among adults with

anxiety disorders (Otto et al. 2001). The strength and specificity of the relationship between early SAD and subsequent risk for panic (or depression) remain unclear, however, because of the relative lack of longer-term prospective study designs. In one notable exception, among a community-based sample of 816 adolescents who were evaluated at age 16 and then followed prospectively until age 30, child-onset SAD was a risk factor for developing adult panic and depressive disorders (Lewinsohn et al. 2008).

Onset of SAD symptoms in childhood may be gradual and insidious, or acute in response to a life stressor or seemingly innocuous illness or event. Early SAD symptoms may be maintained or exacerbated by caregivers' expressed fears or by overprotective or accommodating behaviors (Eisen et al. 2008). For a majority of children with SAD, symptoms may fluctuate or spontaneously remit over time (Foley et al. 2004).

Treatment

Given the prevalence, course, and comorbidity associated with SAD, the relative dearth of empirical research specifically devoted to testing treatments for SAD in childhood, adolescence, or adulthood is noteworthy. To our knowledge, no randomized controlled trials (RCTs) have been conducted to evaluate treatments for SAD in adults. However, children and adolescents with primary or secondary SAD diagnoses have been included in a number of RCTs conducted to evaluate the effectiveness of cognitive-behavioral interventions and medications for anxious youths. These trials typically include children and adolescents with a variety of primary anxiety disorders, including SAD, GAD, social phobia, overanxious disorder (a DSM-III-era near-equivalent of GAD in children and adolescents), and panic disorder. In this section, we briefly review this literature.

In 1994, Kendall reported outcomes for some of the earliest RCT trials comparing cognitive-behavioral therapy (CBT) with wait-list control in youths ages 9–13 with a primary diagnosis of SAD, overanxious disorder, or avoidant disorder (another DSM-III-era anxiety disorder that has now been collapsed into avoidant personality disorder) (Kendall 1994; Kendall et al. 1997). Cognitive interventions included helping children to identify anxious feelings and somatic responses, identify and alter anxious cognitions, modify patterns of self-talk, devise coping plans, and evaluate performance and self-rewards. Behavioral interventions included imaginal and in vivo exposure, relaxation training, and use of contingent reinforcement procedures. In both of these trials, children who were randomly assigned to receive individual CBT showed higher diagnostic recovery rates than did those on wait list, with additional data indicating maintenance of treatment gains 3–7 years posttreatment (Kendall and Southam-Gerow 1996; Kendall et al. 2004). No sub-analyses of findings for SAD per se were reported.

Cartwright-Hatton et al. (2004) systematically reviewed 10 RCTs, estimating that 56% of anxious youths no longer had symptoms that met criteria for their primary anxiety disorder following CBT. Two meta-analyses of CBT trials for anxious youths published in 2007 also supported the efficacy of CBT interventions, with both indicating comparable outcomes for CBT provided in individual or group format. In-Ablon and Schneider (2007) estimated that 69% of anxious youths who completed an acute trial with CBT no longer had symptoms that met cri-

teria for their principal anxiety disorder at posttreatment, as compared with 13% of wait-list controls. However, intention-to-treat analyses provided a more conservative estimate, with 55% of those who had entered CBT treatment showing remission of the primary anxiety disorder. In a 2008 review, Silverman et al. concluded that individual CBT, group CBT, and group CBT with parents were all *probably efficacious* treatments, based on Chambless and Hollon's (1998) criteria (Silverman et al. 2008).

Since 2008, additional trials have added substantial weight to the literature regarding efficacy of CBT for anxious youths. In the largest extant RCT of treatments for anxious youths, the multi-site Child/Adolescent Anxiety Mulitmodel Study (CAMS) trial (Walkup et al. 2008), 488 children ages 7–17 years with a primary diagnosis of SAD, GAD, or social phobia were randomly assigned to receive an acute (up to 12 weeks) course of individual CBT, sertraline (up to a dosage of 200 mg/day), CBT plus sertraline, or pill placebo. In this sample, 3.3% had a primary diagnosis of SAD alone; 6.8% had SAD and social phobia, 8% had SAD and GAD, and 35.9% had SAD, social phobia, and GAD. Primary outcomes indicated that youths who received combination treatment displayed superior clinical improvement as compared with either CBT or sertraline alone. Outcomes for CBT and sertraline monotherapies did not differ, but both therapies were superior to pill placebo, and for both the number needed to treat (NNT) to achieve a response relative to placebo was 3. Estimates of full remission (of all pretreatment anxiety disorders) ranged from 46% to 68% for combination treatment, 34% to 46% for sertraline, 20% to 46% for CBT, and 15% to 27% for placebo (Ginsburg et al. 2011).

The positive benefit of sertraline in the CAMS trial adds to the extant literature supporting the use of SSRIs for childhood anxiety disorders, and specifically SAD (Birmaher et al. 2003; Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001). Rates of adverse events, including suicidal ideation, did not differ in the sertraline group as compared with placebo; although the sertraline group did report higher levels of insomnia, fatigue, sedation, and restlessness/fidgeting as compared with youths who received CBT alone. Notably, the NNT of 3 obtained for sertraline relative to placebo was the same as that identified in a meta-analysis of six RCTs comparing SSRI treatments with pill placebo for anxious youths (Bridge et al. 2007). Thus, current data suggest that SSRIs represent the medication of choice for anxious youths, including those with a primary or secondary diagnosis of SAD.

Other study designs have attempted to identify the importance of parental involvement and extent to which it facilitates CBT outcomes for anxious youths. Indicators of parental depression, anxiety, and family dysfunction have been identified as potential predictors of poor child outcome (Berman et al. 2000; Crawford and Manassis 2001). Thus, a number of trials have attempted to test the differential efficacy of CBT treatments that include family-based therapy work, as compared with typical individual CBT. Family-focused CBT treatments aim to modify maladaptive parental beliefs; teach parents to support child mastery skills and constructively respond to their child's anxiety; facilitate parent-child communication; and, for anxious parents, encourage the use of skills to manage their own levels of anxiety. Results of one trial of 79 youths ages 7–14 years diagnosed with SAD, overanxious dis-

order, or social phobia (Barrett et al. 1996) indicated that younger children (ages 7–10) and girls responded more favorably to CBT plus family management, than to individual CBT.

In another trial (Kendall et al. 2008) of 161 youths ages 7–14 with a principal diagnosis of SAD, GAD, or social phobia, individual CBT and family-based CBT performed similarly with respect to reduction in principal anxiety disorder diagnoses. Both arms outperformed a family-based attentional control condition that provided family psychoeducation and support. In this trial, 38% of the enrolled youths had a mother with one or more anxiety disorders. Children whose mothers had symptoms that met criteria for an anxiety disorder were significantly more likely to retain their principal anxiety disorder diagnosis posttreatment, as compared with children whose mothers were anxiety-free (43% vs. 21%). Secondary analyses of study data indicated that all three treatment groups had improvements in depression and adaptive functioning both at posttreatment and 1-year follow-up (Suveg et al. 2009), supporting the positive impact of alternative family-based interventions on global outcomes among children with SAD.

Additional lesser-studied family or parent-focused treatments have been proposed for the treatment of youths with SAD. Siqueland et al. (2005) proposed a treatment sequence involving individual CBT sessions followed by attachment-based family therapy sessions. These were explicitly aimed at helping adolescents (ages 12–18) with SAD, GAD, or social phobia negotiate greater psychological autonomy from parents, decrease parental use of psychological control, and improve child-parent communication and open discussion of disagreement or conflict without threatening emotional closeness or security of the parent-child relationship. A follow-up study comparing this approach with child CBT demonstrated that CBT was slightly more beneficial than the family-focused approach; anxiety in parents made both approaches less effective (Bodden et al. 2008). Other authors have advocated for SAD-specific psychodynamic treatment models (Muratori et al. 2005) akin to panic-focused psychodynamic psychotherapy (Milrod et al. 2000) for panic disorder, as well as parent child interaction therapy (Choate et al. 2005), or SAD-specific models of parent training (Eisen et al. 2008). While holding potential promise, further research is needed. In addition, future work is needed to determine whether effective SAD treatment will diminish longer-term risk for adult mood and anxiety psychopathology.

Given the historic reluctance to diagnose SAD in adults despite its presence in DSM, the general absence of RCTs evaluating treatments for adult SAD is unsurprising. Current data on comorbid SAD highlight its negative impact within adult psychiatric populations. This includes lower response rates to identical treatment interventions, prolonged time to response in mood disorders, and nonresponse to CBT among panic patients (Aaronson et al. 2008; Boelen 2013; Dell'Osso et al. 2012; Kirsten et al. 2008; Manicavasagar et al. 2000; Miniati et al. 2012). Future research employing prospective, longitudinal study designs is needed to assess the long-term risks associated with adult SAD and to determine whether successful treatment of SAD in adulthood may have longer-term impacts on subsequent levels of mood and anxiety disorder morbidity. Clinically, patients with separation anxiety are profoundly sensitive to transitions and losses, including those experienced within a

therapeutic relationship (Milrod et al. 2014). Separation anxiety is often so ego-syntonic that patients and clinicians may have little awareness of its presence or profound impact, yet it fuels chronic anxiety and a global sense of inadequacy and incompetence that can undermine psychiatric treatments. In psychotherapy, separation anxiety requires the therapist's consistent focus to facilitate its verbal articulation, in order to make change possible. In the absence of an evidence base for treatment of adult SAD, it would seem reasonable to consider adult adaptations of the treatments that have been best established for SAD in youths, namely CBT and SSRI medication.

Conclusion

Inclusion of separation anxiety disorder among the anxiety disorders in DSM-5 represents an important recognition of its presence and impact across the lifespan, and may spur much-needed clinical research into this relatively unstudied population. Research on novel and existing clinical interventions may benefit from being viewed through a lens of separation anxiety, given its early onset and apparent impact. Basic information is sparse, and further research is needed. Future prospective research tracking SAD may uncover differential mechanisms of vulnerability to chronic anxiety, including anxiety profiles that do not respond to standard treatment interventions.

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CHAPTER 18

Social Anxiety Disorder (Social Phobia)

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Social anxiety disorder (SAD), also known as social phobia, encompasses fear and avoidance of social or performance situations, with prominent fear of embarrassment or humiliation (see Box 18–1 for the DSM-5 criteria). The disorder is very common, with a reported lifetime prevalence of 12% (Ruscio et al. 2008). It typically has onset by teenage years and is often chronic.

The scope of feared situations can range from fear of a few specific public performance situations to a more generalized fear of most social situations. In this chapter we review the psychosocial and medication approaches with the strongest evidence base for efficacy in the treatment of SAD.

Box 18–1. DSM-5 Diagnostic Criteria for Social Anxiety Disorder

300.23 (F40.10)

A. Marked fear or anxiety about one or more social situations in which the individual is exposed to possible scrutiny by others. Examples include social interactions (e.g., having a conversation, meeting unfamiliar people), being observed (e.g., eating or drinking), and performing in front of others (e.g., giving a speech).

   Note: In children, the anxiety must occur in peer settings and not just during interactions with adults.

B. The individual fears that he or she will act in a way or show anxiety symptoms that will be negatively evaluated (i.e., will be humiliating or embarrassing; will lead to rejection or offend others).

C. The social situations almost always provoke fear or anxiety.

Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, clinging, shrinking, or failing to speak in social situations.

D. The social situations are avoided or endured with intense fear or anxiety.
E. The fear or anxiety is out of proportion to the actual threat posed by the social situation and to the sociocultural context.
F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 months or more.
G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
H. The fear, anxiety, or avoidance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
I. The fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder, such as panic disorder, body dysmorphic disorder, or autism spectrum disorder.
J. If another medical condition (e.g., Parkinson's disease, obesity, disfigurement from burns or injury) is present, the fear, anxiety, or avoidance is clearly unrelated or is excessive.

Specify if:

Performance only: If the fear is restricted to speaking or performing in public.

Psychotherapies

Cognitive-Behavioral Therapies

Cognitive-behavioral therapy (CBT) has received the most attention of any psychotherapeutic approach to SAD, comprising approximately 70% of the randomized controlled trials in the existing literature. Theoretical models of SAD (Clark and Wells 1995; Heimberg et al. 2010) imply that to successfully reduce social anxiety, treatment must provide patients with the opportunity to reevaluate old and construct new cognitive representations of their social selves. Consistent with these results, the best-supported cognitive behavioral treatment protocols for individuals with SAD involve the combination of correcting maladaptive thinking patterns (i.e., cognitive restructuring) and confronting feared stimuli (i.e., exposure to social situations). Relaxation exercises and social skills training are also commonly used but have less empirical support. (For a comprehensive review of cognitive behavioral techniques for SAD, see Wong et al. 2012.)

Cognitive Restructuring

Individuals with SAD often display problematic thinking patterns (e.g., "They will think I'm weak if my voice shakes") and beliefs (e.g., "If people really knew me, they wouldn't like me"). During *cognitive restructuring*, the therapist and patient collaboratively identify distorted or maladaptive cognitions and challenge them using such strategies as Socratic questioning, logical disputation, and behavioral experiments.

Exposure

Broadly, *exposure* refers to strategies that require contact with the feared situation (e.g., parties, talking to persons in authority, or public speaking). Exposure may be direct, through the use of role-playing or participation in real-life situations, or indirect, such as when feared events are visualized. Exposure provides a context for the natural habituation of unpleasant

physiological arousal, increases contact with reinforcers inherent in the social environment, and provides an opportunity to put negative thoughts and beliefs to a scientific test. Although research supports exposure's efficacy in reducing social anxiety (e.g., Al-Kubaisy et al. 1992), there is recent evidence that exposure coupled with cognitive restructuring techniques that directly address maladaptive cognitions is more efficacious in terms of both short-term and long-term outcomes than exposure alone in the treatment of SAD (Ougrin 2011).

A large body of research supports the efficacy of CBT for SAD. Several empirically supported treatment protocols have been developed in both group (Heimberg and Becker 2002) and individual (Clark et al. 2003; Hope et al. 2010) formats. Treatment duration typically ranges from 12 to 20 weeks. One of the most researched and widely disseminated treatments for SAD is Heimberg's cognitive-behavioral group therapy (CBGT; Heimberg and Becker 2002). Treatment components include 1) psychoeducation about the factors associated with the onset and maintenance of social fears; 2) exposure to increasingly challenging situations, both inside and outside of sessions; 3) cognitive restructuring to help patients become more aware of distorted thinking patterns, challenge maladaptive thoughts, and implement more helpful ways of thinking about feared situations; and 4) homework assignments to read relevant materials or conduct out-of-session exposures. Compared with educational-supportive group therapy, CBGT produces greater reductions in anxiety, both during a behavioral test and as assessed through clinical interview (Heimberg et al. 1990), and treatment gains are better maintained after 5 years (Heimberg et al. 1993). Heimberg and colleagues have since adapted CBGT to an individual format and added cognitive restructuring activities directed toward the modification of core beliefs about the self, the world, and the future (Hope et al. 2010). The individual protocol produces effect sizes similar to those for the group protocol (Ledley et al. 2009).

A similar treatment with some distinct features is Clark's individual cognitive therapy (CT) for SAD. Controlled trials of this protocol have also yielded large effect sizes (Clark et al. 2003). CT includes exposure and cognitive restructuring, with emphasis on identifying and eliminating of subtle forms of avoidance (i.e., safety behaviors), such as going to a party but speaking only to a close friend. In CT, the therapist and patient create a personalized conceptualization of the factors serving to maintain the patient's social anxiety (e.g., the patient's idiosyncratic thoughts, images, safety behaviors, and attentional strategies). Throughout therapy, the patient's negatively distorted self-representations are modified using video feedback in which predicted performance is compared with actual performance. Additionally, the therapist encourages direction of attention away from aversive internal experiences (i.e., symptoms of anxiety) and toward the task at hand. CT has demonstrated efficacy for individuals with SAD (Clark et al. 2003), and the gains made during CT tend to be maintained when individuals are assessed at 5-year follow-up (Mörtberg et al. 2011).

Although the current evidence best supports the use of exposure techniques coupled with cognitive restructuring (Ougrin 2011), other psychosocial interventions, such as mindfulness-based therapies and interpersonal therapies, also show considerable promise. Well-controlled research is still relatively scant, but a few studies comparing these newer treatments to traditional CBT have emerged in recent years.

Mindfulness and Acceptance-Based Therapies

Mindfulness and acceptance-based therapies, such as mindfulness-based stress reduction (MBSR; Kabat-Zinn 1990) and mindfulness-based cognitive therapy (MBCT; Segal et al. 2002), are increasingly being used to treat a variety of psychological disorders, including SAD. These techniques emphasize present moment focus and a nonjudgmental awareness of cognitive, emotional, and physiological processes. Mindfulness techniques such as mindful meditation, body scans, and breath-focused attention are used to facilitate present-focused attention and reduce sympathetic nervous system reactions. Additionally, patients are taught that emotional distress is largely the product, not the cause, of reflexive cognitive and behavioral attempts to control or banish negative internal experience (i.e., experiential avoidance). Thus, the major goal of therapy is to help patients stay focused in the present moment and give up the struggle to control painful thoughts and feelings, resulting in greater self-acceptance.

Two randomized trials have compared mindfulness-based treatments with CBT. Koszycki et al. (2007) compared MBSR, which was not designed to directly target social concerns, with CBGT for SAD (Heimberg and Becker 2002). Both treatments were found to be effective, but CBGT led to greater reductions in self- and clinician-rated social anxiety as well as higher rates of response and remission. Piet et al. (2010) conducted a pilot study comparing MBCT with traditional CBGT in socially anxious young adults and found that the treatments were not significantly different from each other (although CBGT produced larger effects).

In summary, mindfulness-based treatments are likely less efficacious than CBT, but with typical programs lasting only 8 weeks, they may represent a useful low-cost treatment alternative for SAD. The integration of CBT and mindfulness techniques has yet to be investigated.

Interpersonal and Psychodynamic Psychotherapy

Interpersonal psychotherapy (IPT), which was originally developed for treating unipolar depression, focuses on modifying dysfunctional patterns in interpersonal relationships. Like CBT, IPT is a time-limited therapy, typically lasting 12–16 weeks. J.D. Lipsitz, J.C. Markowitz, and S. Cherry (Manual for interpersonal psychotherapy of social phobia, unpublished manuscript, 1997) tailored IPT for social anxiety. In the Lipsitz et al. treatment, after selecting a key focus (e.g., loss or role transition), the therapist helps the patient develop an understanding of the connection between anxiety symptoms and current interpersonal problems and use this understanding to improve both. IPT techniques such as reassurance, clarification of emotional states, and role-playing are used to increase interpersonal flexibility and expand the patient's behavioral repertoire.

An open trial of IPT for SAD found that 78% of the participants were classified as treatment responders (Lipsitz et al. 1999). However, in a follow-up trial that compared IPT with a credible placebo therapy, the groups showed similar rates of improvement (Lipsitz et al. 2008). A second randomized trial of Norwegian

psychiatric inpatients (Borge et al. 2008) provides stronger support for the use of IPT in treating SAD. In this study, residential CT (based on Clark's individual CT) was compared with residential IPT, based on the manual of Lipsitz et al. (1999). Both treatments were equally efficacious; however, several aspects of this study may limit the generalizability of results. The inpatients tended to have chronic and highly comorbid symptom presentations, and many had tried alternative treatments without success. Additionally, this study adapted Clark's CT for an inpatient sample even though this form of CT has been studied almost exclusively in outpatient settings. A third randomized trial (Stangier et al. 2011) attempted to correct the methodological shortcomings of the previous study by comparing IPT, CT, and a wait-list condition in an outpatient setting. Both IPT and CT led to considerable improvements over the wait-list group; however, CT was more effective than IPT in reducing symptoms of social anxiety and resulted in significantly better treatment response immediately after treatment and at 1-year follow-up. Thus, although findings have been mixed, current evidence suggests that IPT is an effective therapy for SAD but should not trump CBT as a first-line treatment.

Psychodynamic psychotherapy for SAD has been little studied. However, Gabbard (2014) suggested that SAD is associated with several unconscious desires and emotions that could be directly targeted through psychodynamic treatment. He hypothesized that patients with SAD experience shame as a result of an unconscious desire to be the center of attention and guilt as a result of the unconscious desire to eliminate social competition. According to this perspective, individuals with SAD may have internalized the representations of significant attachment figures who were critical, shaming, or abandoning. Therefore, in psychodynamic psychotherapy, therapists encourage patients to explore how contact with such figures may have shaped their expectations about the likelihood of negative judgment or abandonment.

Two randomized trials examining the efficacy of psychodynamic therapy for SAD have been conducted. Knijnik and colleagues (2004) compared psychodynamic group treatment (PGT) with a credible control intervention and demonstrated that PGT resulted in greater reductions in social anxiety symptoms. More recently, Leichsenring et al. (2013) completed a large-scale multisite trial comparing manualized forms of psychodynamic therapy and CBT with a wait-list group. Psychodynamic therapy was superior to wait list and equivalent to CBT on the measure of treatment response, but it did not perform as well as CBT on the index of remission and on several dimensional measures related to social anxiety. These trials suggest promise for manualized psychodynamic approaches, but further study is required.

Medication and Other Biological Therapies

A substantial body of evidence has demonstrated efficacy of several classes of medications for SAD. Well-controlled trials include studies of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), irreversible and reversible monoamine oxidase inhibitors (MAOIs), and, to a lesser extent, benzodiazepines, β-adrenergic blockers, mirtazapine, gabapentin, and pregabalin. Most of the patients in these clinical trials had general-

ized social fears, so the relevance of much of this literature for persons with SAD that is limited to performance situations is less clear.

SSRIs and the SNRI Venlafaxine

SSRIs have emerged as the first-line medication treatment for SAD on the basis of more than 20 randomized placebo-controlled trials of five different SSRIs. Another six placebo-controlled trials support the efficacy of the SNRI venlafaxine. Paroxetine, sertraline, fluvoxamine, and venlafaxine have each received U.S. Food and Drug Administration approval in the United States for the indication of SAD, and fluoxetine, citalopram, and escitalopram have also been studied in randomized clinical trials. In short-term (8–12 week) clinical trials of these medications, response rates based on Clinical Global Impression ratings of much improved or very much improved have typically ranged from 40% to 70% (e.g., M.B. Stein et al. 1998). These rates are generally 20%–30% greater than corresponding placebo response rates. A recent meta-analysis reported that relative to placebo, treatment response was superior for the SSRIs (N=19 studies; relative risk of response [RR]=1.69; 95% CI 1.49, 1.90; total sample N=4,615) and for venlafaxine (N=4; RR=1.59; 95% CI 138, 1.83; N=1,173) (Ipser et al. 2008).

Treatment dosages are similar to those used for depression (e.g., median effective paroxetine dosage 20 mg/day), although optimal dosing for a specific patient may vary within the approved ranges. The time course of acute response may be slower than that seen in depression, with most responses occurring by the eighth week of treatment but with some further responses and further improvement accruing through week 12 and beyond (D.J. Stein et al. 2002). No single drug in this class has been demonstrated to be superior to another in direct comparisons, though fluoxetine is the only SSRI with some negative findings in controlled trials.

SSRIs offer advantages of a relatively mild adverse effect profile, safety in overdose or with concurrent use of alcohol, and a broad spectrum of efficacy for comorbid anxiety and affective disorders. Drawbacks include delayed response and common adverse effects that have the potential to exacerbate some problems already common in SAD, such as increased sweating or sexual dysfunction.

SAD patients who respond to initial SSRI treatment are commonly treated for 6–12 months or longer. Responders after a year of treatment may show further improvement after a second year of treatment (D.J. Stein et al. 2003). Placebo-controlled discontinuation studies show that following acute response, maintenance treatments of 6 months or greater significantly decrease the chance of relapse, although in some studies more than 50% of responders to acute treatment have been able to maintain that response after drug discontinuation (e.g., D.J. Stein et al. 2002).

Benzodiazepines

Among the benzodiazepines, clonazepam has the most evidence for efficacy in SAD. Davidson et al. (1993) completed a double-blind placebo-controlled study of clonazepam in 75 patients. After 10 weeks of treatment, 78% of those taking clonazepam (mean dosage 2.4 mg/day) and 20% of those receiving placebo were rated as at least moderately improved. In another randomized clinical trial, clonazepam and cognitive-behavioral group

therapy were equally effective after 12 weeks of treatment (Otto et al. 2000). In a placebo-controlled discontinuation trial among SAD patients effectively treated with clonazepam, 79% were able to tolerate slow taper (0.25 mg reduction every 2 weeks) and discontinuation without relapse in the short term (Connor et al. 1998). Similar efficacy was reported for bromazepam. Alprazolam, however, did not differ from placebo on most measures in one trial, and at 2-month follow-up most patients had lost most of their gains (Gelernter et al. 1991). Although benzodiazepines have not been systematically studied in nongeneralized SAD, they are often used clinically on an as-needed basis for performance anxiety, and they represent an alternative to β-adrenergic blockers for these patients. A drawback of as-needed use is that patients may develop psychological dependence on the medication.

Benzodiazepines offer advantages of rapid onset and good tolerability. Disadvantages include lack of efficacy for comorbid depression, risk of abuse, contraindication in the presence of comorbid substance abuse, potential adverse effects on cognition and coordination, and routine development of physiological dependence requiring slow taper when the drug is to be discontinued. A small study of coadministration of clonazepam with an SSRI demonstrated a trend for the combination to be superior to an SSRI alone (Seedat and Stein 2004), which is consistent with clinical experience of clonazepam as a useful augmentation strategy for partial responders to SSRIs.

Clonazepam appears to be most effective when given on a standing-dose basis, typically at a total daily dose of 2–4 mg. The medication should be initiated at 0.25–0.5 mg once daily at bedtime, and the dosage can be gradually increased on a twice-a-day schedule. The most common adverse effect is sedation, which usually abates within several days after a dosage increase. Patients should be warned against abrupt discontinuation because of the risk of withdrawal symptoms, including seizures.

Monoamine Oxidase Inhibitors

MAOIs were the first class of medications to be extensively studied for SAD. The efficacy of phenelzine, an irreversible inhibitor of monoamine oxidase, has been established in four double-blind placebo-controlled studies. Open trials have reported response rates of 79% for tranylcypromine, another irreversible MAOI (Versiani et al. 1988), but low-dose selegiline (≤10 mg/day) appeared ineffective for most patients (Simpson et al. 1998).

Although phenelzine appears to be at least as efficacious as the SSRIs for SAD, the irreversible MAOIs remain a second- or third-line treatment because of dietary restrictions and adverse effects. The low-tyramine diet prohibits most cheeses and a variety of other foods, beer, and red wines, and sympathomimetic medications must also be avoided. SSRIs must be allowed to "wash out" for 2 weeks (5 weeks for fluoxetine) before an MAOI is initiated because of the risk of serotonin syndrome. Common adverse effects at effective dosages (usually 45–90 mg/day) of phenelzine include postural hypotension, sedation, sexual dysfunction, and weight gain.

Two reversible inhibitors of monoamine oxidase, brofaromine and moclobemide, have a safety profile superior to that of irreversible MAOIs. Brofaromine appeared efficacious for SAD in three controlled trials, but it has never been marketed. Moclobemide has been widely marketed outside of the United

States but appeared efficacious in only three out of five placebo-controlled trials (Bonnet 2003). Meta-analyses have found that moclobemide is significantly less efficacious than the SSRIs and the irreversible MAOIs (Blanco et al. 2003).

Beta-Adrenergic Blockers

Beta-blockers have appeared effective for performance anxiety in numerous nonpatient samples of performers, but they have not proven superior to placebo in several controlled trials of daily use in patients with primarily generalized SAD (e.g., Liebowitz et al. 1992). Despite these negative findings for generalized SAD, β-blockers such as propranolol are often clinically effective when used in single doses (10–40 mg for propranolol) as needed for performance anxiety in SAD.

Propranolol is typically given in a 10–40 mg dose 1 hour prior to the performance situation, and effects typically last a few hours. Patients may be encouraged to first take a test dose at home to allay any fears about tolerability and to test whether dosage is adequate to block an exercise-induced increase in heart rate.

Buspirone

Buspirone has appeared ineffective at low dosages (≤30 mg/day) in controlled trials for SAD (e.g., van Vliet et al. 1997). Open-trial data (Schneier et al. 1993) suggest that buspirone may be more effective at dosages of 45 mg/day or greater or as augmentation of partial responders to SSRIs.

Gabapentin and Pregabalin

Gabapentin and pregabalin, which have been reported to act via the $\alpha_2\delta$ subunit of voltage-sensitive calcium channels, have each appeared efficacious in a single controlled trial. Gabapentin 900–3,600 mg/day reduced SAD severity more than placebo, but only 32% of the patients had more than a 50% reduction in social anxiety symptoms (Pande et al. 1999), suggesting that gabapentin's efficacy may be modest. Pregabalin 600 mg/day (but not 150 mg/day) decreased social anxiety symptoms and achieved a higher global response rate compared with placebo (43% versus 22%). Somnolence and dizziness were the most common adverse effects (Pande et al. 2004).

Atypical Antipsychotics

The antipsychotics olanzapine and quetiapine have not been demonstrated efficacious in very small controlled trials and at present have little role in the treatment of SAD. In the olanzapine study, response rates for medication and placebo did not differ significantly, but olanzapine-treated patients had significantly superior outcomes on social anxiety–specific scales (Barnett et al. 2002). In a study of 15 patients randomly assigned to receive 8 weeks of treatment with quetiapine 400 mg or placebo, there were no significant group differences on either of two primary outcome measures; however, 40% of quetiapine patients and 0% of the placebo patients were considered responders (Vaishvani et al. 2007). These studies were small, with limited power to detect clinically meaningful drug-placebo differences. Another study of quetiapine reported that single 25 mg doses taken 1 hour before a public speaking challenge were not effective in preventing SAD symptoms in persons with fear of public speaking. Notably, this class of medications carries a relatively high risk of adverse effects, and there have also been multiple case reports of the *emergence* of

SAD symptoms during treatment of other disorders with antipsychotic medications (Scahill et al. 2003).

Other Agents

Limited data from open trials or very small controlled trials suggest possible efficacy for several other medications, including the antidepressants nefazodone and bupropion and the anticonvulsants topiramate and valproate. Lack of efficacy has been reported for the anticonvulsant levetiracetam, the selective norepinephrine inhibitor atomoxetine, and St. John's wort in single controlled trials.

SAD With Comorbid Conditions

A few studies have addressed pharmacotherapy of persons with SAD and common comorbid conditions. In patients with SAD and comorbid depression, depressive symptoms have been observed to respond more rapidly than SAD symptoms to an open trial of SSRI treatment (Schneier et al. 2003). Persons with SAD and pathological sweating (hyperhidrosis) were shown to benefit from augmentation of SSRI treatment with botulinum toxin treatment for sweating in a randomized controlled trial (RCT; Connor et al. 2006), and uncontrolled studies have suggested the utility of topical application of 20% aluminum chloride or even surgery with endoscopic thoracic sympathicotomy. In an RCT among patients with SAD and comorbid alcohol use disorders, the SSRI paroxetine was efficacious for symptoms of SAD but did not reduce alcohol consumption (Book et al. 2008). Although atomoxetine appeared ineffective for noncomorbid SAD, an RCT in adults with SAD comorbid with attention-deficit/hyperactivity disorder (ADHD) found that atomoxetine monotherapy improved both ADHD and SAD symptoms more than did placebo in this group of comorbid patients (Adler et al. 2009).

Comparison and Integration of Medication and Psychotherapy

Several studies have examined the relative efficacy of CBT and medications for SAD. Heimberg et al. (1998) compared CBGT with phenelzine and two control conditions (pill placebo and educational-supportive group therapy). After 12 weeks, CBGT and phenelzine produced equivalent response rates, which were superior to those of the control conditions. Although phenelzine produced more immediate gains and greater effects on some measures, CBGT patients were less likely than phenelzine patients to relapse over the course of 6 months of maintenance treatment and 6 months of follow-up (Liebowitz et al. 1999). Blomhoff and colleagues (2001) conducted a placebo-controlled trial of 24 weeks of exposure (12 weeks of physician-facilitated exposure plus 12 weeks of self-exposure), sertraline, and a combination of both. All active treatment conditions were superior to placebo at 12 weeks. At 24 weeks, only the sertraline group was superior to placebo. However, by 1-year follow-up, exposure patients had improved, whereas those receiving sertraline or the combination treatment (all of whom had the option to continue sertraline treatment with their general practitioner) had deteriorated on some mea-

sures (Haug et al. 2003). It is important to note that the physicians administering the first 12 weeks of exposure had minimal training in CBT, making interpretation of the results complicated.

Two randomized trials have examined the efficacy of fluoxetine in comparison or combination with CBT. Clark and colleagues (2003) compared their CT protocol with fluoxetine and placebo (both with self-exposure instructions). CT outperformed the other conditions, and these differences were maintained at 1-year follow-up. However, fluoxetine failed to surpass placebo. In contrast, a study by Davidson and colleagues (2004), which compared a variant of CBGT, fluoxetine, CBGT plus fluoxetine, and CBGT plus placebo, found no differences between these conditions, all of which were superior to placebo alone.

Most recently, Blanco and colleagues (2010) compared CBGT with phenelzine, a combination of CBGT and phenelzine, and pill placebo in 128 patients with SAD. Combined treatment was significantly more efficacious than placebo, but surprisingly, this was not consistently the case for phenelzine or CBGT alone.

Thus, it appears that CBT and pharmacological treatments have similar efficacy for SAD. However, each may confer unique benefits. Medication has been associated with more rapid anxiety reduction (e.g., Heimberg et al. 1998), but gains made in CBT have been better maintained (e.g., Liebowitz et al. 1999). To date, it is unclear whether combining pharmacotherapy with CBT confers any benefit above the use of either treatment alone.

Although the vast majority of combined treatment research has utilized CBT, one study examined the combination of PGT and clonazepam versus clonazepam alone (Knijnik et al. 2008). Unfortunately, the findings were mixed and difficult to interpret. Although the combination group demonstrated greater global improvements than the clonazepam-only group, social anxiety symptom reductions were equivalent in both groups. More well-controlled studies must be conducted, with different classes of medications, to determine whether combining psychodynamic therapy and medication confers any additional benefit over medication alone.

Treatment Selection

In considering an initial treatment for the patient with SAD, CBT has the advantage of potentially producing more enduring improvement than medication therapies (an important consideration in this highly chronic condition), and it has safety advantages, especially in women who may anticipate pregnancy or breast-feeding. Medication may be the preferred first-line treatment option for SAD patients who are unable or unwilling to engage in CBT, have had an inadequate response to CBT, or who prefer a medication approach. Combined medication and psychotherapeutic treatment may yield synergistic benefits for some patients, though further study is needed to delineate how to best combine treatments and predict which patients will do best with such an approach.

Conclusion

Recent studies have established the efficacy of several treatment techniques for SAD. The best-established approaches include several forms of CBT and SSRIs or venlafaxine. Alternative medications include the MAOI phenelzine, the ben-

zodiazepine clonazepam, and for non-generalized SAD, β-adrenergic blockers. Alternative psychotherapies include interpersonal therapy and mindfulness and acceptance-based therapies.

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CHAPTER 19

Generalized Anxiety Disorder

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Generalized anxiety disorder (GAD) is a chronic and highly comorbid illness characterized by excessive and uncontrollable worry (Box 19–1). It is marked by a later onset than other anxiety disorders (Kessler et al. 2005) and is associated with fluctuations in symptom severity and impairment (e.g., Wittchen et al. 2000). It demonstrates both a low probability of recovery (32%–58%) and a high likelihood of recurrence (45%–52%) (Rodriguez et al. 2006) over a 2- to 12-year period. GAD is associated with significant disability and impairment comparable to pure major depressive disorder (Hoffman et al. 2008) and can be more debilitating than pure substance use disorders, some anxiety disorders, and personality disorders, even after controlling for sociodemographic variables and comorbid conditions (Grant et al. 2005).

Box 19–1. DSM-5 Diagnostic Criteria for Generalized Anxiety Disorder

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A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B. The individual finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):

Note: Only one item is required in children.

1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).

F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Individuals with GAD attempt to enhance their sense of control or preparedness through anticipation of negative outcomes or worst-case scenarios. They scan their environment for potential danger and negatively interpret neutral or ambiguous stimuli as threatening (Mathews and MacLeod 1994). Because of their lack of present moment focus, these individuals tend to ignore information in their immediate surroundings that could potentially challenge their distorted views (Borkovec and Newman 1998), which triggers emotional distress. This emotional distress is associated with many somatic features, including restlessness, fatigue, irritability, concentration difficulties, muscle tension, and sleep disturbance. Overall, GAD is a serious and costly mental illness with regard to degree of distress, disability and subsequent loss of work productivity, and quality of life (Newman 2000). Thus, targeted interventions are necessary to effectively address core symptoms and associated features.

In this chapter we discuss several empirically established approaches to treatment for GAD, including conventional cognitive-behavioral therapy (CBT), pharmacotherapy, psychodynamic psychotherapy, and integrative psychotherapy.

A Cognitive-Behavioral Approach to Treating GAD

Because maladaptive patterns of thoughts and behaviors can be viewed as central to GAD, CBT has been extensively tested and has demonstrated efficacy; it is currently the best-established psychotherapeutic treatment for GAD. Within a CBT framework, change is promoted through identifying early anxiety triggers, challenging and disrupting individuals' misconceptions and factors maintaining worry, actively testing the validity of erroneous beliefs, using modified desensitization methods, reducing avoidance behaviors, improving skills to manage worry and anxiety, and developing more adaptive ways of responding to neutral and ambiguous situations (e.g., Newman et al. 2006).

The initial steps in treatment involve educating patients about their symptoms and treatment goals in order to promote positive expectations and thereby enhance outcomes (Newman and Fisher 2010). Patients are then asked to engage in self-monitoring to recognize shifts in internal state and triggers for that state and to identify maladaptive patterns when reacting to perceived threats. Through this process, patients draw connections between their worries and their somatic states (e.g., muscle tension), distorted thoughts, and external triggers.

Once responses to perceived threats are identified, patients are asked to maintain a present focus and develop and implement cognitive, imagery, relaxation, and behavioral interventions to combat their habitual responses (Newman and Borkovec 2002). Cognitive restructuring involves learning the association between thoughts and emotions, identifying cognitive errors, and replacing these distortions with more accurate thoughts. Therapists then ask patients to practice challenging these cognitive distortions in their daily lives.

In addition to cognitive restructuring, relaxation techniques are used to address elevated anxiety. Patients are typically instructed to relax a series of muscle groups and engage in breathing exercises during and between sessions (Newman and Borkovec 2002). Coupling their thoughts with their autonomic state, patients are asked to simultaneously "let go" of their worries while they relax. Once patients have mastered relaxation, those techniques are combined with aversive imagery using self-control desensitization (SCD). In SCD, patients imagine themselves encountering a worry trigger, and when they become anxious, they focus on relaxing away their stress response.

Borkovec and Ruscio (2001) evaluated the efficacy of CBT via a meta-analysis of 13 randomized controlled trials (RCTs) of CBT for GAD and found consistent outcomes across the studies. Although meta-analyses are limited by the quality of studies included, they generally adhere to uniformly applied criteria when selecting studies in attempts to reduce bias. Moreover, the validity of Borkovec and Ruscio's findings was strengthened by incorporating studies that selected participants whose symptoms met the diagnostic criteria for GAD, included follow-up assessments 6–24 months posttreatment, and reported low attrition rates. Additionally, most studies used treatment protocols ($n=9$ studies), conducted adherence checks ($n=8$ studies), and measured nonspecific factors such as therapy expectancy and credibility ($n=8$ studies). CBT significantly reduced anxiety symptoms by posttreatment (mean $d=2.48$), and gains were maintained for up to 2 years (mean $d=2.44$). CBT was also superior both to a wait list and no treatment ($d=1.09$) and to placebo psychotherapy at posttreatment ($d=0.71$) and follow-up ($d=0.30$). CBT was also superior to both cognitive therapy and behavior therapy alone at posttreatment ($d=0.26$) and follow-up ($d=0.54$).

Two more recent meta-analyses (Covin et al. 2008; Hanrahan et al. 2013) also examined the efficacy of CBT and yielded findings similar to those of Borkovec and Ruscio. Covin et al. (2008) found that individual CBT ($d=1.72$) was more effective than group CBT ($d=0.91$), and the effect of CBT on worry was larger for young adults ($d=1.69$) than for older adults ($d=0.82$). CBT is also effective for children with anxiety disorders. For example, In-Albon and Schneider (2007) compared CBT for childhood anxiety disorders (ex-

cluding posttraumatic stress disorder and obsessive-compulsive disorder) with alternative therapies and control conditions. However, these investigators included studies (n=24 studies) in which participants met diagnostic criteria for a variety of anxiety disorders, and they did not differentiate between anxiety disorders. They found that active CBT (d=0.86) was superior to a wait-list control condition (d=0.13). Individual and group therapy were also equally effective in children at posttreatment and follow-up, but results were mixed regarding the incremental efficacy of a parent-focused treatment component.

Interpersonal and Emotional Processing Deficits in GAD

Dyadic relationships form a centerpiece to development, and disturbances in relationships commonly underlie anxiety and mood disorders. Interpersonal processes have been implicated in the development and maintenance of anxiety disorders. Individuals with GAD exhibit a heterogeneous variety of interpersonal problems marked by intrusive, exploitable, cold, and nonassertive characteristics (Przeworski et al. 2011). They are more likely to have enmeshed relationships or to engage in role reversal, such as the child or adolescent assuming parental responsibility (see, e.g., Cassidy and Shaver 1999), and they report a predominance of worry about interpersonal concerns and conflicts (Breitholtz et al. 1999). GAD is also more commonly associated with marital discord or dissatisfaction than any other anxiety disorder (Whisman 1999).These interpersonal areas of concern predict negative CBT outcomes, higher dropout rates, and reduced probability of remission (Borkovec et al. 2002).

Furthermore, individuals with GAD report greater sensitivity to negative emotion (Llera and Newman 2010), increased emotional intensity (Mennin et al. 2005), and increased reactivity to negative emotional expression in others (Erickson and Newman 2007) when compared with individuals without anxiety.

Integrative Therapies

Several therapies have addressed these interpersonal and emotional processing deficits by adding interpersonal and emotional techniques to conventional CBT. Newman and colleagues (2004) developed an integrated treatment protocol that incorporates cognitive-behavioral, interpersonal, and emotion-based interventions with the aims of identifying dysfunctional relationship patterns and enhancing emotional processing (Newman et al. 2004). Findings from a randomized controlled trial comparing CBT plus supportive listening (n=40) with CBT plus interpersonal/emotional processing therapy (I/EP; n=43), using an additive design, indicated that both treatments were effective in reducing symptoms and that this symptom reduction was maintained at 2-year follow-up. In addition, 69% of patients in the integrative treatment and 53% of patients receiving CBT achieved high end-state functioning at 2-year follow-up (Newman et al. 2011). The efficacy of I/EP might be improved by recent conceptualizations that individuals with GAD may use worry not to avoid emotion but rather to brace themselves for a potential negative outcome (see Newman and Llera 2011; Newman et al. 2013 for a complete review). This provides conceptual support for an additional exposure-based treatment for

GAD, such that individuals with GAD can be exposed to negative emotional contrasts by eliciting a relaxed state prior to emotional exposure.

The conceptualization of worry as a cognitive avoidance strategy (Borkovec et al. 2004) helped to motivate the development of other therapies. Targeting the heightened emotional intensity and maladaptive emotion regulation strategies characteristic of GAD, emotion regulation therapy proposes to address emotional avoidance through the integration of emotional components into a cognitive-behavioral framework (Mennin et al. 2006). Acceptance and commitment therapy (ACT) also aims to reduce reliance on emotional avoidance strategies, as well as decrease individuals' negative interpretations of their thoughts and increase their ability to enact behavioral change that conforms to their values and to focus on the here and now (Roemer et al. 2008). In a controlled examination of the efficacy of acceptance-based therapy for GAD, patients were randomly assigned to receive immediate ($n=15$) or delayed ($n=16$) treatment. ACT significantly reduced clinician-rated and self-reported GAD symptoms. Seventy-eight percent of participants no longer had symptoms that met criteria for GAD, and 77% achieved high end-state functioning at posttreatment (Roemer et al. 2008). This improvement was maintained at 3- and 6-month follow-up.

Psychodynamic Psychotherapy

Ambivalence and difficulties with early attachments are theorized to play a role in the development and maintenance of GAD. In the absence of secure attachment during early developmental periods, individuals may view the world as threatening, uncontrollable, and unpredictable and underestimate their ability to cope with perceived stressors (Bowlby 1982). To enhance their sense of control, they may develop perfectionistic tendencies, seek excessive approval from others, and require constant reassurance regarding their worries. They may also present as self-conscious and overly conformist. Psychodynamic treatments for GAD have focused on patients' inability to tolerate letting their guard down and the insecure relational dynamics characteristic of GAD.

Crits-Christoph and colleagues (1995) developed a short-term dynamic treatment for GAD based on supportive-expressive therapy (SET; Luborsky 2000). The SET model of GAD suggests that early traumatic events can influence the development of *schemas*, or mental representations of self, others, and the world, especially schemas about others' ability to successfully meet the interpersonal needs of individuals with GAD. Accordingly, these individuals may exhibit uncertainty regarding the attainment of love, stability, security, and protection. Worry serves a defensive function for individuals with GAD, who are fearful of potential negative outcomes, leading them to avoid thinking about more emotionally salient issues (Borkovec et al. 2004). This avoidance perpetuates worry and maladaptive relational patterns.

Founded on a modified form of psychoanalytic principles, SET is guided by delineation of a core conflictual relationship theme (CCRT), which comprises 1) the wishes and needs of the GAD patient, 2) responses of the other, and 3) subsequent responses of the patient. The CCRT is not equivalent to the psychoanalytic concept of transference. In fact, the emphasis on CCRT distinguishes

SET from traditional psychodynamic psychotherapy. SET works by helping patients to identify the CCRT across various areas of their lives and to understand how it relates to the anxiety they experience. In SET, both supportive and expressive (insight-oriented) techniques are used to help deepen patients' understanding of their relationships and their connection to their anxiety. Patients also learn improved ways of coping with their feelings, expressing their needs, and responding to others. SET also emphasizes development of a positive therapeutic alliance to address emotional sequelae of an insecure attachment style.

In an open trial of brief SET (i.e., 16 weeks) for GAD, Crits-Christoph and colleagues (1996) found that treatment significantly reduced participants' anxiety, worry, and interpersonal problems, thereby providing preliminary support for this brief psychodynamic psychotherapy for GAD. Leichsenring et al. (2009) further validated these results in an RCT, in which SET was found to result in significant improvement in GAD symptoms and interpersonal problems.

Pharmacotherapy

Among the first medications with demonstrated efficacy were the γ-aminobutyric acid (GABA) agonist benzodiazepines, such as alprazolam, diazepam, and lorazepam. Response rates in placebo-controlled trials have ranged from 45% to 66% (Baldwin et al. 2011a; Lydiard and Monnier 2004) with effect sizes across studies of 0.38 (Hidalgo et al. 2007). Although these medications are rapidly effective in short-term use, long-term use of these medications is controversial because of the potential for tolerance, dependence, withdrawal symptoms, sedation, and motor and cognitive abnormalities (Lydiard and Monnier 2004). Accordingly, benzodiazepines are mostly recommended for treatment of acute anxiety symptoms.

Given safety concerns related to benzodiazepines, selective serotonin reuptake inhibitors (SSRIs) have been considered first-line pharmacological treatment (Katzman et al. 2011). Earlier studies indicated that buspirone (e.g., Rickels et al. 1982), a 5-HT_{1A} partial agonist, and imipramine (e.g., Rickels et al. 1993), a tricyclic antidepressant, demonstrated efficacy in treating GAD. Subsequently, the SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been shown to be efficacious for GAD on the basis of more than 20 randomized placebo-controlled trials. The SNRIs venlafaxine XR and duloxetine were demonstrated efficacious, with 60%–80% response rates for venlafaxine and 52%–65% response rates for duloxetine (e.g., Baldwin et al. 2011a). In controlled trials of SSRIs, response rates were between 62% and 81% for paroxetine and 52% and 78% for escitalopram, with a mean response rate of 63% in adult studies overall (Baldwin et al. 2011a; Lydiard and Monnier 2004). Overall effect size was 0.36 for the SSRI treatments (Hidalgo et al. 2007). The relative efficacy of different medications for GAD is not well established; however, in a recent meta-analysis fluoxetine was ranked first for response and remission, and sertraline was ranked first for tolerability, which was higher than that of the SNRI treatments (Baldwin et al. 2011b).

Pregabalin, a GABA analogue that inhibits the release of excitatory neurotransmitters, has demonstrated efficacy for GAD in randomized placebo-controlled trials. It has been approved by the U.S. Food and Drug Administration for the treatment of seizures and fibro-

myalgia in the United States and was recently approved for the treatment of GAD in the European Union. Across studies, response rates for pregabalin ranged from 44% to 61%, although some studies did not find significant differences from placebo (Baldwin et al. 2011a; Lydiard and Monnier 2004). A recent meta-analysis found an overall effect size of 0.36 across seven placebo-controlled trials (Boschen 2011).

Comparative Efficacy of Treatments for GAD

Controlled investigations have compared CBT, psychodynamic therapy, and pharmacotherapy in the treatment of GAD. For example, Durham et al. (1994) and Leichsenring et al. (2009) tested forms of psychodynamic treatment against CBT for GAD. Durham and colleagues (1994) compared a nonmanualized analytic therapy with manualized cognitive therapy (CT) and anxiety management training. Although CT appeared to be more effective than analytic psychotherapy, the lack of a manualized psychoanalytic treatment, lack of training of analytic therapists prior to the trial, and lack of evaluation of therapist adherence critically limited this study.

To help correct for nonequal comparisons, Leichsenring and colleagues (2009) compared manualized supportive-expressive therapy (SET) with CBT in the treatment of GAD. The treatments did not differ on the primary anxiety outcome measure, two additional measures of anxiety, and a measure of interpersonal dysfunction, although effect sizes at posttreatment and 6-month follow-up favored CBT over SET for GAD. However, CBT was superior to SET on measures of trait anxiety, worry, and depression. The latter findings may highlight CBT's core targeting of maladaptive thought processes such as worry. Nevertheless, given the very limited scientific literature evaluating efficacy of any form of dynamic therapy for GAD and the narrow range of the SET intervention for GAD in comparison with the wider range of dynamic therapy, it is premature to make definitive claims about differential efficacy.

In a comparison of the effectiveness of CBT versus pharmacotherapy for GAD, a meta-analysis that incorporated 65 controlled studies and used random effects modeling (Mitte 2005) revealed no significant differences in the effect sizes for anxiety reduction in CBT trials versus pharmacotherapy, suggesting no differences in efficacy between these two treatment types. However, attrition rates were higher in pharmacotherapy, indicating that CBT may be better tolerated. Notably, most of the pharmacotherapy studies in this comparison used benzodiazepines, which have demonstrated rapid short-term effects but less usefulness over time. There are only two small controlled studies directly examining combined pharmacotherapy plus CBT for GAD (Bond et al. 2002; Power et al. 1990), with mixed results. Specifically, Power and colleagues found that all CBT conditions (i.e., CBT alone, CBT plus placebo, and CBT plus diazepam) were superior to diazepam and placebo conditions in reducing GAD symptoms. Conversely, Bond and colleagues examined brief psychotherapy (i.e., anxiety management training or nondirective therapy) combined with buspirone or placebo in the treatment of GAD. They reported no significant differences between treatment groups, with all groups demonstrating significant improvement in symptoms. Neither of these studies examined SSRI

or SNRI medications. For GAD in adults, unlike for other anxiety disorders, there have been no collaborative trials of CBT and pharmacotherapy comparing the efficacy of the best-established forms of each treatment. However, the Child/Adolescent Anxiety Multimodal Study (CAMS; Ginsburg et al. 2011), a multisite clinical trial, examined the effect of sertraline alone, CBT alone, CBT plus sertraline, and clinical management with pill placebo in children and adolescents with separation, social, and/or generalized anxiety disorder. Participants in the CBT plus sertraline condition had significantly higher rates of remission than other conditions. This study incorporated a generalized treatment protocol and aggregated across anxiety disorders. Furthermore, one recent study offered individuals seeking SNRI treatment the option of additional CBT and found no additive effect beyond those treated with SNRIs alone who had refused CBT treatment (Crits-Christoph et al. 2011).

When a decision is being made regarding a course of treatment for GAD, it is important to consider the benefits and limitations of various treatment approaches. CBT is typically delivered over a relatively short period of time (e.g., 16 weeks), exhibits long-term effects, and teaches skills that can be used in everyday life, but it does not typically focus on interpersonal issues. Accordingly, treatment providers may opt to conduct integrative treatments or brief dynamic therapy to focus on relational dynamics. However, psychotherapeutic approaches in general require more of a time commitment on the part of the patient. In CBT, for example, a patient must not only attend weekly sessions for at least several months but also participate in between-session homework. Conversely, pharmacotherapy is fast acting and effective in reducing acute anxiety. However, evidence suggests that the magnitude of these benefits may be lower for GAD than for other anxiety disorders (Hidalgo et al. 2007). While taking medication such as SSRIs, patients may experience significant side effects, which can include nervousness, sexual dysfunction, weight gain, drowsiness, and sleep problems (Baldwin et al. 2011a). Also, patients may require ongoing treatment to maintain benefits of medication. Therefore, it is important to consider and discuss all treatment options.

Comorbidity is an important issue in the treatment of GAD. Little is known about how CBT, psychodynamic psychotherapy, and pharmacotherapy compare in their effects on comorbidity as it relates to outcomes for GAD. However, CBT for GAD led to decreased rates of comorbid anxiety disorders and dysthymia (Borkovec et al. 1995; Newman et al. 2010). Also, presence of personality disorders predicted better outcome from nonmanualized brief psychodynamic psychotherapy than from SSRIs or SNRIs (Ferrero et al. 2007). Antidepressants are preferred over anxiolytics in part because of their broader efficacy in treating frequently comorbid mood disorders. Further research is needed to clarify how each of the therapies is affected by comorbidity.

Although randomized controlled trials have demonstrated the utility of many therapies in reducing GAD symptoms through clinically significant change, they are not effective for everybody (Newman and Borkovec 2002). Therefore, it is important not only to determine the most efficacious and long-lasting treatments for GAD and to consider maintenance treatment to enhance response and remission rates, but also to improve short-term treatments to boost acute-phase functioning and increase compliance.

Conclusion

The severity and pervasiveness of GAD, its fluctuating course, and the degree of associated functional impairment underscore the need for effective treatments. Various psychological and pharmacological treatments for GAD target specific cognitive, behavioral, affective, interpersonal, and physiological processes that have been implicated in the development and maintenance of this disorder. CBT, the most well established psychotherapy for GAD, generally includes such interventions as self-monitoring, relaxation training, and cognitive therapy directed toward negative appraisals. The efficacy of CBT in reducing core and related symptoms of GAD has been extensively documented in a series of randomized controlled trials. Investigations into the efficacy of CBT typically reveal average high-end-state functioning (i.e., no longer meeting criteria for GAD) in about 50% of participants. Therefore, conventional CBT models have been enhanced through incorporation of interpersonal, mindfulness, and emotional techniques to address additional areas of dysfunction not typically targeted in CBT protocols. To date, integrative psychotherapy for GAD has been more successful in reducing anxiety symptoms and associated features, as demonstrated by increased rates of remission.

Likewise, brief psychodynamic psychotherapy for GAD (e.g., SET) has centered on elucidating patients' recurrent maladaptive relationship patterns and their relationship to their worry and anxiety. Although the one extant comparative efficacy study favored CBT over SET, empirical investigation of various models of psychodynamic treatment for GAD is still in its infancy.

Pharmacotherapy is another empirically established form of treatment for GAD. It can be used alone or in combination with psychotherapy and is effective in addressing acute worry and anxiety. The preferred pharmacotherapies of SSRIs or SNRIs are broadly effective for treating frequently comorbid depression.

Despite short- and long-term gains following various therapeutic interventions for GAD, treatments are being further developed and refined by conducting additive and dismantling designs that examine incremental validity of individual treatment components, exploring moderators and mediators of treatment, and investigating mechanisms of change across treatment approaches.

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CHAPTER 20

Specific Phobia

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DSM-5 (American Psychiatric Association 2013) recognizes four subtypes of specific phobia, including animal (e.g., dogs, cats, cockroaches, snakes), natural environment (e.g., heights, water, storms), blood-injection-injury (e.g., injections, blood tests), and situational (e.g., enclosed spaces, driving, airplanes). A fifth category, "other," includes such phobias as fear of choking or vomiting that do not fit into one of the four categories (see Box 20–1 for DSM-5 diagnostic criteria for specific phobia).

Among the most common psychiatric disorders, specific phobia has a lifetime prevalence of 12.5% (Kessler et al. 2005). In community (Depla et al. 2008) and clinical (Lipsitz et al. 2002) samples, multiple phobias are common. Multiple phobias often are not limited to a single subtype; DSM-5 indicates that all appropriate subtypes should be endorsed. However, people typically seek treatment for one type of phobia, and treatment is generally focused on only one phobia. In this way, treatment planning for specific phobia differs from planning for some other anxiety disorders (e.g., agoraphobia, social phobia) or for obsessive-compulsive disorder, for which the full range of symptoms associated with that diagnosis are generally targeted together.

Box 20–1. DSM-5 Diagnostic Criteria for Specific Phobia

A. Marked fear or anxiety about a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood).

   Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, or clinging.

B. The phobic object or situation almost always provokes immediate fear or anxiety.
C. The phobic object or situation is actively avoided or endured with intense fear or anxiety.
D. The fear or anxiety is out of proportion to the actual danger posed by the specific object or situation and to the sociocultural context.
E. The fear, anxiety, or avoidance is persistent, typically lasting for 6 months or more.

F. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
G. The disturbance is not better explained by the symptoms of another mental disorder, including fear, anxiety, and avoidance of situations associated with panic-like symptoms or other incapacitating symptoms (as in agoraphobia); objects or situations related to obsessions (as in obsessive-compulsive disorder); reminders of traumatic events (as in posttraumatic stress disorder); separation from home or attachment figures (as in separation anxiety disorder); or social situations (as in social anxiety disorder).

Specify if:

Code based on the phobic stimulus:

300.29 (F40.218) Animal (e.g., spiders, insects, dogs).

300.29 (F40.228) Natural environment (e.g., heights, storms, water).

300.29 (F40.23x) Blood-injection-injury (e.g., needles, invasive medical procedures).

Coding note: Select specific ICD-10-CM code as follows: **F40.230** fear of blood; **F40.231** fear of injections and transfusions; **F40.232** fear of other medical care; or **F40.233** fear of injury.

300.29 (F40.248) Situational (e.g., airplanes, elevators, enclosed places).

300.29 (F40.298) Other (e.g., situations that may lead to choking or vomiting; in children, e.g., loud sounds or costumed characters).

Coding note: When more than one phobic stimulus is present, code all ICD-10-CM codes that apply (e.g., for fear of snakes and flying, F40.218 specific phobia, animal, and F40.248 specific phobia, situational).

In treatment studies, severity and change of specific phobia are often assessed using a behavioral approach test (BAT) in which the individual is observed physically approaching the feared object or situation and rated on avoidance (physical proximity), subjective distress during the task (a distress severity self-rating), and possibly measures of physiological arousal. The advantage of the BAT is that it relies on an observable reaction in the feared situation rather than on the more abstract interpretation inherent in the self-report scales. However, the BAT may fail to capture important aspects of the real-life impact of the fear. Therefore, self-report scales such as the Fear Survey Schedule (Wolpe and Lang 1964) or scales for specific types of phobias, such as the Spider Phobia Questionnaire (Watts and Sharrock 1984), may be used to provide a more complete clinical picture of severity and change over time.

Despite the availability of efficacious psychological treatments, only a very small percentage of individuals with specific phobia seek treatment for this disorder (Brown et al. 2001). This may be in part because the circumscribed nature of specific phobia may lead to only limited and periodic difficulties. However, even individuals with severe disability may avoid treatment because of stigma and embarrassment (Lipsitz et al. 2001).

In early psychoanalytic conceptualizations, phobias were viewed as expressions of underlying conflicts displaced onto external objects or situations, and it was believed that resolution of these conflicts, through in-depth psychotherapy, was necessary and sufficient to resolve the phobia (Freud 1909/1955). A major shift in thinking was prompted by the work of Watson and Rayner (1920), who demonstrated that a phobic response could be "learned" by a small child ("Little Albert") by simultaneously and re-

peatedly presenting a previously neutral stimulus and an aversive stimulus (i.e., classical conditioning). This suggested that aversive learning experiences might explain some phobic fears and that associations could also be unlearned. Later, Mary Cover Jones demonstrated that a learned fear response could be stopped by pairing the aversive stimulus with a positive stimulus (Jones 1924).

Some decades later, Joseph Wolpe introduced the first formal clinical treatment approach for phobias, which he called *systematic desensitization* (Wolpe 1968). In this treatment, the feared stimulus was called up in imagination while the patient implemented deep muscle relaxation, which was thought to suppress the anxiety reaction. Five controlled clinical studies of systematic desensitization were reviewed by Choy and colleagues (Choy et al. 2007). Most showed some positive effects on subjective anxiety, but effects on avoidance were mixed. It is also difficult to gauge long-term effects of systematic desensitization because studies assessed outcome following treatment with a behavioral approach test, which constituted a real rather than an imagined exposure. Evidence gradually accumulated showing an advantage for real exposure to the feared situations over exposure in imagination. There was little evidence that deep muscle relaxation improved effects of exposure, and this approach prolonged and complicated the treatment, which could increase dropouts.

Exposure Therapy

Overview

A preference has developed for gradual exposure, which allows the patient to confront and master increasingly fearful situations in manageable steps. During exposure-based treatment (also known as *in vivo exposure* or *graduated exposure*), the patient gradually confronts phobic stimuli of increasing levels of intensity. Initial exposure exercises are often done with the therapist; additional exposure exercises are done through homework without the presence of the therapist. A detailed description of exposure-based phobia treatment is provided in a number of manuals (e.g., Antony and Swinson 2000). Here I briefly summarize its components.

Exposure therapy begins with psychoeducation about the phobic response, symptoms, and maintaining factors. The therapist and patient then create a fear hierarchy, identifying various feared situations related to the phobia and ranking them in terms of anxiety and desire to avoid so that exposure exercises can progress from less feared to more feared situations. During each exposure the patient is encouraged to remain in contact with the object or situation long enough for anxiety to noticeably decrease. One study showed, for example, that exposures lasting at least 1 minute are more effective than those that are terminated while the patient is still at a high level of anxiety (Marshall 1985). Exposures are repeated for each situation with sufficient regularity for anxiety to decrease.

Exposure therapy for specific phobia is among the clearest success stories of behavior therapy. A systematic review (Choy et al. 2007) and a meta-analysis (Wolitzky-Taylor et al. 2008) of clinical trials of exposure therapy conclude that this approach is efficacious compared with no treatment and with other treatments, including systematic desensitization and vicarious exposure. Response rates range to as high as 80%–90% (Choy et al. 2007), with large effect sizes compared with wait-list groups and moderate

effect sizes compared with nonspecific treatments (Wolitzky-Taylor et al. 2008). Benefits of exposure therapy are robust with studies including all phobia subtypes and outcomes and include decreased anxiety and avoidance on the basis of behavioral approach tests and self-report scales. Many methodologically strong studies are available. Although most studies did not address clinically significant change (Jacobson et al. 1984), the few that did indicate that change is clinically meaningful (Öst et al. 1997). A single limitation is that most analyses are based on treatment completers. Although most studies boast high retention, dropout is higher in some studies (e.g., studies of dental phobia).

Can gains from a brief psychological treatment be maintained over longer periods? Choy and colleagues reviewed 16 studies with follow-up of 6–14 months and concluded that gains were maintained or further improved in nearly all studies (Choy et al. 2007). In their meta-analysis, Wolitzky-Taylor et al. (2008) found that effect size of exposure-based treatment versus placebo was larger at long-term outcome than at posttreatment. However, longer-term follow-up of several years found that a substantial minority of patients with successful initial response to treatment for phobias had recurrence in subsequent years (Lipsitz et al. 1999), suggesting that there is somewhat more variability in long-term outcome than was initially believed. One potential predictor of maintenance versus relapse is frequency of continued exposure; a limitation is that few studies document whether patients continue exposure and to what degree. Studies for which continued exposure was explicitly recommended (e.g., Hellström and Öst 1996) reported very good long-term outcome. Another factor that appears to predict better long-term outcome is carrying out exposure in multiple contexts and with varying types of stimuli (e.g., heights in different buildings from different vantage points) (Rowe and Craske 1998). Recognizing the possibility of relapse, Öst suggested that prior to termination clinicians should 1) encourage continued exposure over the long term, 2) help patients anticipate and prepare for setbacks, and 3) rehearse coping strategies in the event that setbacks occur (Öst 1989a).

Innovations in Delivery of Exposure Therapy

One-Session Exposure Therapy

Early experimentation with abrupt, intense exposure treatment known as *flooding* yielded some positive results (e.g., Boulougouris et al. 1971), but this approach was less efficacious and less well tolerated than graduated exposure. However, Öst demonstrated that the benefits of graduated exposure could be accomplished in a one prolonged (i.e., 3 hour) session treatment with good outcome (e.g., Öst 1989b). Results of a meta-analysis suggested that one-session exposure may be slightly less efficacious than multiple sessions (Wolitzky-Taylor et al. 2008). However, this approach provides some clear advantages over standard graduated exposure in terms of increased compliance and reduced costs (Davis et al. 2012).

Self-Guided and Computer-Assisted Treatment

Given the relative simplicity of exposure exercises and the need to proceed systematically and repeatedly along the phobia hierarchy, professionals treating specific phobia seem to find self-guided or manual-guided therapies particularly appeal-

ing. In an early comparison of therapist-guided and self-guided therapy using written manuals, Hellström and Öst (1995) found that therapist involvement provided a clear advantage. However, computer-administered treatments have been found to be as beneficial as therapist-assisted exposure for a number of phobic conditions (e.g., Marks et al. 2004), and a recent meta-analysis found no difference between computer-assisted and therapist exposure therapy for a phobia group (Cuijpers et al. 2009). Because of increased flexibility and potential for human feedback, recent work along these lines in other anxiety disorders has focused on Internet-based therapies.

Exposure Through Virtual Reality

In addition to challenges of therapist time, it is difficult for therapists to re-create or accompany patients to some phobic situations. Pioneered by Rothbaum and colleagues, virtual reality exposure therapy (VRET) uses virtual reality technology to enhance the reality experience of the situation. VRET seems to have a clear advantage over imaginal exposure (e.g., Wiederhold and Wiederhold 2003), and the conclusions of one meta-analysis suggest possible superiority over real exposure (Powers and Emmelkamp 2008; Rothbaum et al. 1995). However, other meta-analyses (e.g., Opris et al. 2012) suggest roughly equivalent benefits to real exposure, and a systematic review (Meyerbröker and Emmelkamp 2010) noted some limitations in research on VRET to date. However, evidence of lower refusal rate with VRET compared with real exposure (Garcia-Palacios et al. 2007) and increasingly affordable programmability of VRET technology suggest great promise for treatment of phobias. Augmented reality, which allows real-world view along with virtual reality elements, may enhance generalization of virtual exposure learning to real-world situations (Botella et al. 2010).

Additional Psychological Interventions

In addition to exposure-based interventions, other strategies have also been studied for treating phobias. These strategies are typically combined with exposure, but some may also have independent benefit.

Cognitive Therapy

Because cognitive factors seem to play a role in etiology and maintenance of specific phobia (Thorpe and Salkovskis 1995), research has examined cognitive strategies that seek to reduce fear by addressing these factors. Cognitive strategies may begin with something as basic as providing corrective information about the feared situation (e.g., showing statistics about safety of airplane travel) to help counteract irrational beliefs. However, this typically entails systematically identifying, monitoring, and challenging cognitive errors such as overgeneralization (e.g., I was bitten by a dog, so all dogs are likely to bite), catastrophizing (focusing on the worst case scenario), and probability overestimation (e.g., because dogs have been known to bite, every dog presents a serious threat of biting). Results for specific phobia have suggested some benefit, although not consistently so, for cognitive interventions alone (Choy et al. 2007) but no clear benefit for the addition of cognitive restructuring to exposure therapy (Wolitzky-Taylor et al. 2008).

Anxiety Management Strategies

Because exposure tends to evoke intense anxiety, therapists may incorporate a range of anxiety management strategies, including breathing retraining, applied muscle relaxation, and distraction. Relaxation techniques, such as those originally used in systematic desensitization, may help reduce anxiety temporarily and have been examined in various forms for treatment of phobias. These techniques are controversial, however, because the emotional processing model of fear reduction (Foa and Kozak 1986) presumes that attentional focusing and sufficient physiological arousal may be needed to activate and engage the fear structure and allow for emotional processing. This would suggest that such techniques as distraction and relaxation may preclude optimal emotional processing. Summarizing the evidence to date, there is little evidence that adding relaxation to exposure therapy increases efficacy (Öst et al. 1984), but there is some evidence of short-term benefit (e.g., Lukins et al. 1997) and little evidence that it undermines exposure's benefits. Similar conclusions can be drawn regarding distraction (Rodriguez and Craske 1993). In a review of several studies comparing distraction with attentional focus for a range of specific phobias, there was no evidence for benefit of strict attentional focus (Schmid-Leuz et al. 2007).

Reducing Safety Behaviors

Increasing attention has been paid to the important role of *safety behaviors.* Safety behaviors reflect subtle avoidance strategies aimed at decreasing possible negative outcomes from feared stimuli. Thus, an individual may appear to be confronting the feared situations but instead is employing subtle behaviors intended to reduce risk (e.g., keeping hands in pockets during exposure to a dog). This may reduce the full experience of "exposure" and preclude the ability to disconfirm beliefs regarding potential adverse consequences (Salkovskis 1991).

Interoceptive Exposure

A key component of cognitive-behavioral treatment of panic disorder, interoceptive exposure involves systematic exposure to feared internal sensations rather than to external situations or objects (Barlow et al. 1989). This technique presumes that the internal symptoms are themselves powerful triggers or amplifiers of anxiety and that defusing these triggers can prevent more intense anxiety or panic. Situational phobias, such as claustrophobia, are characterized by occurrence of full-symptom situational panic attacks and prominent physical symptoms of panic attacks. As such, overcoming these fears may require systematic exposure and habituation to physical symptoms, which themselves become triggers for increased fear and avoidance. Supporting this notion, Craske and colleagues (1995) found that treatment that included focus on disconfirmation of misappraisals of bodily sensations was beneficial for individuals with claustrophobia but not for those with spider phobia.

Applied Muscle Tension

One possible exception to the consistently strong benefits of simple exposure-based therapy is blood-injection-injury phobia. Öst and colleagues (1991) found that blood phobia treated with exposure produced only modest benefits after 1 year. Öst therefore developed a specific strategy, applied tension, to help

overcome the atypical vasovagal response that commonly occurs in blood-injection-injury phobias. Applied tension entails first learning and practicing repeated contractions of large muscle groups, which helps prevent or attenuate the drop in blood pressure, and then gradually performing these contractions while being exposed to phobia triggers. This technique has been found to be an efficacious treatment for blood-injection-injury phobias in a number of trials (e.g., Öst et al. 1991).

Reducing Fear Versus Disgust

In most phobias, anxiety is characterized by fear focused on possible danger or harm. However, some phobias are more closely tied with disgust. In blood-injection-injury phobias (Sawchuk et al. 2002), phobia of insects and reptiles (Olatunji et al. 2010), and emetophobia (Lipsitz et al. 2001), feelings of disgust are prominent. Disgust can also be reduced by exposure, but Smits and colleagues (2002) found that fear and disgust decrease in different patterns during successful treatment.

Hypnotherapy and Eye Movement Desensitization and Reprocessing

Although often used in clinical practice, two therapy approaches are viewed as somewhat controversial for treatment of phobias. Hypnotherapy seeks to alter consciousness and improve suggestibility so that patients can undertake steps they might otherwise refuse. The few controlled studies of hypnotherapy have produced mixed findings (e.g., Hammarstrand et al. 1995), and there is some evidence that immediate gains, if obtained, are not well maintained (Moore et al. 2002). Eye movement desensitization and reprocessing (EMDR; Shapiro 1999), which involves eye movement exercises along with imaginal exposure, has been more extensively researched for specific phobia, and it appears to reduce subjective anxiety (e.g., Kleinknecht and Lenz 1989). Evidence is less strong for change in phobia avoidance, however, and benefits appear to be similar to those of imaginal exposure without eye movements (Sanderson and Carpenter 1992) and somewhat less robust than those of exposure-based therapy (e.g., Muris and Merckelbach 1997).

Medication Treatment

In stark contrast to other anxiety disorders, medications have yet to demonstrate prolonged efficacy for treatment of specific phobia (Choy et al. 2007). Wilhem and Roth (1997), for example, found that a dose of alprazolam prior to flying significantly reduced phobic anxiety compared with placebo. However, during a subsequent flight without medication, the group receiving medication had greater anxiety than the placebo group. In a study of dental phobia, a single dose of midazolam produced similar anxiety reduction as brief stress management with imaginal exposure, but 3 months later the benefits of relaxation continued, while benefits of medication were not sustained (Thom et al. 2000). Because some individuals encounter phobic situations only rarely, medications may be used each time the individual enters the situation, such as dental work or magnetic resonance imaging (Murphy and Brunberg 1997).

A few studies have examined whether medication could enhance effects of psychological treatment such as exposure. Some early studies examined effects of,

for example, benzodiazepines during exposure (Whitehead et al. 1978) and found no benefit. A comparison of behavior and supportive therapy with imipramine versus placebo also showed no advantage for phobia conditions (Zitrin et al. 1978), although ceiling effects may have limited the ability to detect benefits. Because these compounds may exert a more direct effect on subjective anxiety per se, they may facilitate exposure but block processes involved in extinction or emotional processing.

A promising development is the use of D-cycloserine (DCS), a partial agonist at the *N*-methyl-D-aspartate receptor. Ressler and colleagues (2004) compared phobic individuals undergoing exposure with and without DCS and found that patients receiving DCS had greater reduction in nearly all phobia-related variables measured. These benefits were maintained at 3-month follow-up. A recent meta-analysis (Norberg et al. 2008) found that results support the initial findings that DCS enhances effects of exposure therapy, although benefits decrease over repeated administrations and there is evidence of some attenuation of benefit at follow-up.

Conclusion

Exposure therapy is the treatment of choice for specific phobia. Long-term outcome, although perhaps not as clear-cut as once thought, is positive. Furthermore, such techniques as recommendations for continued exposure practice may help improve long-term outcome. Cognitive restructuring, a central strategy in some other anxiety disorders, appears to be less crucial in treatment of specific phobias. Anxiety management strategies, such as relaxation and distraction, are used by some therapists to help manage acute anxiety, and there is little evidence that they undermine the benefits of exposure.

Medications, although valuable for short-term management of acute anxiety, have not demonstrated efficacy for treatment of specific phobia. D-Cycloserine may increase speed of effect in exposure therapy, although given the high success of exposure therapy in increasingly short treatments, its clinical relevance is unclear.

The most important challenge remaining in specific phobia is to increase the proportion of individuals who avail themselves of efficacious treatments. Technological developments, such as computer-guided treatment and virtual reality, may help clinicians meet this challenge.

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CHAPTER 21

Obsessive-Compulsive Disorder

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Obsessive-compulsive disorder (OCD) is characterized by recurrent and persistent thoughts, urges, or images (obsessions) that are experienced, at some time during the disturbance, as intrusive and unwanted and by repetitive behaviors or mental acts (rituals or compulsions) that the person feels compelled to perform to lessen anxiety or discomfort (Rasmussen and Eisen 1989) (see Box 21–1 for criteria). Many treatments have been attempted for chronic and severe disorders such as OCD, but until recently, OCD was unresponsive to most remedies. Specific psychotherapeutic, pharmacological, and other somatic treatments, however, now have established efficacy for this condition.

Box 21–1. DSM-5 Diagnostic Criteria for Obsessive-Compulsive Disorder

300.3 (F42)

A. Presence of obsessions, compulsions, or both:

Obsessions are defined by (1) and (2):

1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.
2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).

Compulsions are defined by (1) and (2):

1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.

2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.
   Note: Young children may not be able to articulate the aims of these behaviors or mental acts.

B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder; stereotypies, as in stereotypic movement disorder; ritualized eating behavior, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control, and conduct disorders; guilty ruminations, as in major depressive disorder; thought insertion or delusional preoccupations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).

Specify if:

With good or fair insight: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true.

With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true.

With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true.

Specify if:

Tic-related: The individual has a current or past history of a tic disorder.

Psychotherapies

Behavioral Therapy

In 1966, Meyer reported the successful behavioral treatment of two patients with severe compulsive ritualizing through around-the-clock response (or ritual) prevention (Meyer 1966). A series of elegant studies by other investigators (Foa et al. 1998; Marks et al. 1975; Rachman et al. 1973; Steketee et al. 1982) confirmed that approximately 75% of patients with OCD will engage in behavioral therapy and that most who do so faithfully show both acute (Foa et al. 2005; Pediatric OCD Treatment Study [POTS] Team 2004) and sustained (O'Sullivan et al. 1991) improvement (i.e., >25% reduction in symptom severity). Unsuccessful treatment is most often a result of noncompliance, which may take the form of unrecognized mental rituals. Comorbid severe depression, misdiagnosis (e.g., when psychotic delusions are misinterpreted as obsessions), and state-dependent learning (usually associated with high doses of central nervous system depressant substances such as alcohol or benzodiazepines) also interfere with response to behavioral therapy. Wolpe's (1958) systematic desensitization

was found to have weak efficacy for patients with OCD (Cooper et al. 1965). Relaxation did not increase the benefit of exposure and ritual prevention, and exposure in fantasy or imagination was not as effective as exposure in real life (in vivo) (Steketee et al. 1982).

Effective behavioral therapy for OCD consists of *exposure* and *ritual prevention* (Abramowitz 1996). These simple concepts, systematically applied, lead to *habituation* of anxiety associated with obsessions so that rituals are no longer necessary to reduce anxiety. As with many things in life, Mark Twain summarized it well: "Do the thing you fear most and the death of fear is certain." This commonsense approach has often been tried by patients on their own but imperfectly and ineffectively. The task of behavioral therapy is to provide a structure in which these basic principles are brought into effective practice.

A critical phase of behavioral therapy for OCD is psychoeducation because patients vary widely in their initial willingness to directly confront their fears in therapy. Patients should be informed that their anxiety level may *increase* initially during exposure sessions and that this anxiety and the time they must expend are the short-term costs of behavioral therapy, which produces long-term gains of reduced anxiety and dysfunction (Figure 21–1). An analogy with surgery, which produces short-term pain in the process of providing long-term gain, can be helpful.

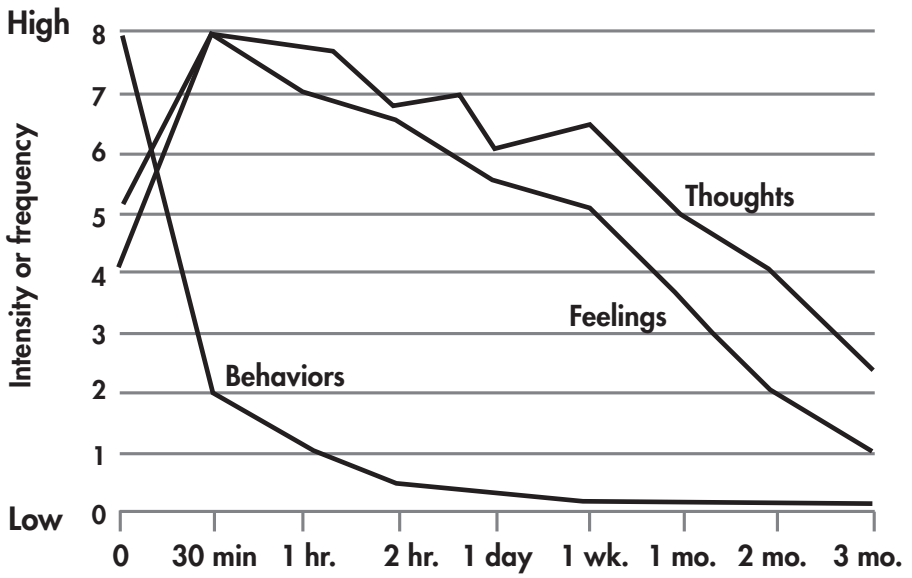

FIGURE 21–1. Sample rates of change with behavioral therapy of an obsessive-compulsive disorder ritual.

Source. Reprinted from Baer L: *Getting Control: Overcoming Your Obsessions and Compulsions,* Revised Edition. Boston, MA, Little, Brown, 2000, p. 53. Copyright 2000. Used with permission.

The cognitive-affective lag, relative to the rapid behavioral change reflected in Figure 21–1, is common; this phenomenon should be explained to patients so

that they expect it and are not surprised by their early reduction in rituals but delayed reduction in obsessions and anxiety.

Rituals (repetitive, intentional, purposeful behaviors or mental thoughts or acts) are performed because they momentarily reduce discomfort and the urge to ritualize. Ritual prevention is also effective in reducing urge and discomfort and does so enduringly but requires a longer time to achieve similar reductions. With ritual prevention, patients with OCD begin to learn through the process of habituation that they can control discomfort from obsessions without performing rituals. This demonstration of anxiety or discomfort reduction, when repeated through systematic exposure and ritual prevention "homework" assignments, frees patients from dependence on rituals. A challenge of the behavior therapist is to design exposures that are stressful enough to robustly activate obsessive fears without jeopardizing the patient's willingness to adhere to prevention of compulsions. Several patient guides to behavioral therapy are available (Baer 2012; Foa and Wilson 2001; Neziroglu and Yaryura-Tobias 1997; Steketee and White 1990). These manuals, coupled with therapist willingness to conduct behavioral therapy with patients who are obsessive-compulsive, often lead to remarkably positive results.

About 25% of patients with OCD referred for behavioral therapy openly decline treatment, and others are only partly compliant, as with all treatments. Far more therapists, including psychologists who espouse behavioral therapy for OCD, fail to employ or emphasize exposure and ritual prevention, the proven elements in cognitive-behavioral therapy (CBT), instead offering cognitive restructuring and ineffective relaxation. BT STEPS, a computer program to guide patients in self-help homework exposure and ritual prevention treatment for OCD, was found to be as helpful in the 64% of patients who completed at least one session as 12 hours of clinician-directed exposure and ritual prevention, and both were significantly more effective than relaxation in this randomized controlled trial (Greist et al. 2002). This program is presently available in Web-based format from Waypoint Health Innovations (http://waypointhealth.com).

Cognitive Therapy

Cognitive therapists seek to change thoughts, feelings, and behaviors. They hypothesize that faulty cognitions permit and then maintain unpleasant affects and dysfunctional behaviors. Correcting faulty cognitions should lead to more agreeable affects and more functional behaviors. However, it is striking that in OCD, patients with insight have repeatedly called their cognitions "crazy," family members have argued against their obsessional fears, and clinicians have agreed that their worries are unfounded, all without benefit.

Reviews (Deacon and Abramowitz 2004; van Balkom et al. 1998) have documented efficacy for cognitive procedures that address faulty risk assessment and exaggerated sense of responsibility. Whether cognitive therapy achieves its benefits directly through cognitive means or indirectly by invoking exposure and ritual prevention (see "Behavioral Therapy" section above) is an important and as yet unresolved question.

Psychodynamic Psychotherapy

Despite Freud's clinical description of his treatment of the "Rat Man," a man suffering from severe borderline panic disorder and OCD, using current nosology,

psychoanalytic approaches have not been studied systematically. Gabbard (2005) acknowledged that "there is little evidence in the literature to suggest that dynamic psychotherapy or psychoanalysis is effective in the treatment of obsessive-compulsive disorder" (p. 993). On the other hand, he quite appropriately emphasized that a psychodynamic perspective can often be a useful adjunct in the overall treatment of OCD, especially to enhance compliance with other treatments and to address interpersonal problems.

Supportive psychotherapy, including establishment of a therapeutic alliance, empathy, minimization of limitations, support for strengths, explanations regarding pathophysiology, tolerance of negative affect, and optimism about improvement, is appropriate for all patients.

Pharmacotherapy

Potent Serotonin Reuptake Inhibitors

Clomipramine

Numerous positive open trials of the potent serotonin reuptake inhibitor (SRI) clomipramine in OCD were followed by at least 22 controlled trials in which clomipramine was either more effective than placebo or tricyclic comparators (11 trials) or equally as effective as selective serotonin reuptake inhibitor (SSRI) comparators (5 trials) (Greist et al. 1995). Clinical opinion has generally led to dosing at the higher end of the dosing range for these agents, although fixed-dose trials, when available, have usually found a flat dose-response curve, suggesting that many patients receive more medication than necessary. Side effects of clomipramine are typical of a tricyclic antidepressant and include anticholinergic, antihistaminergic, and α-adrenergic blocking effects.

Selective Serotonin Reuptake Inhibitors

Multicenter placebo-controlled parallel-design trials of fluoxetine (Tollefson et al. 1994), fluvoxamine (Greist 1992), sertraline (Greist 1992), and paroxetine (Wheadon et al. 1993) and a controlled trial of citalopram (Montgomery et al. 2001) have all found the active compound significantly more effective than placebo. As with clomipramine, onset of improvement was often delayed, with significant differences emerging only between 2 and 6 weeks and continuing to increase for at least 10 weeks. Trials of fluoxetine, sertraline, and paroxetine compared fixed doses, whereas the clomipramine and fluvoxamine trials used an ascending-dose design (average final dosages of 227 and 249 mg/day, respectively). Although there were trends toward greater improvement with increasing dosages of fluoxetine (20, 40, and 60 mg/day) and sertraline (50, 100, and 200 mg/day), no statistically significant differences were seen. Paroxetine was significantly more effective than placebo at 40 and 60 mg/day but not at 20 mg/day.

Although SSRIs have fewer side effects than clomipramine, it is surprising that dropout rates for side effects were not greater in the U.S. Food and Drug Administration (FDA) registration multicenter clomipramine trials (8%) than in the fluoxetine (12%), fluvoxamine (15%), or sertraline (10%) trials. Delayed or inhibited orgasm is a common side effect of the potent SRIs, including clomipramine. Concerns about increased suicidal thoughts and behaviors have led to a class warning for all antidepressants,

including those with OCD indications. Overall, the side effect burden of clomipramine is greater than that of SSRIs, although individual tolerability also varies across SSRIs.

As of 2014, clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline have FDA indications for OCD in adults, and clomipramine, fluoxetine, fluvoxamine, and sertraline also have indications for pediatric populations of various ages. Other SSRIs and serotonin-norepinephrine reuptake inhibitors have demonstrated efficacy in OCD but do not have FDA approval.

Comparative Efficacy of Potent SRIs

Efficacy studies in OCD have consistently employed the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al. 1989). Five items assess time, interference, discomfort, and attempt to control and success in controlling both obsessions and compulsions with scores of 0–4 for each item, providing a total range from 0 to 40. A meta-analysis of the FDA registration multicenter controlled trials of clomipramine, fluoxetine, fluvoxamine, and sertraline found clomipramine to be more efficacious than the SSRIs, which did not differ from each another in efficacy (Figure 21–2) (Greist et al. 1995).

Indirect comparisons have limitations and must be viewed with caution, but double-blind, head-to-head comparisons of clomipramine versus SSRIs are unmasked to some degree by tricyclic side effects. Some studies have found comparable efficacy of SSRIs compared with clomipramine (Bisserbe et al. 1997; Koran et al. 1996; Zohar and Judge 1996), while other studies show at least trends favoring clomipramine (López-Ibor et al. 1996). Most meta-analyses (Ackerman and Greenland 2002; Greist et al. 1995; Kobak et al. 1998; Piccinelli et al. 1995; Serretti et al. 1999; Stein et al. 1995) of adult OCD SRI treatments have found clomipramine to be more efficacious, but this advantage must be balanced against the greater side effect burden of clomipramine.

Duration of SRI Pharmacotherapy

All reports of extended pharmacotherapy with potent SRIs indicate maintenance of or increase in short-term gains for many months. Few discontinuation studies are available, but patients seem to relapse rapidly whenever potent SRIs are discontinued (Pato et al. 1988; Ravizza et al. 1999). Patients must continue to take SRIs to maintain gains achieved, although downward titration to determine an optimal dose (maximum benefit with minimum side effects) is appropriate.

Nonresponse to SRI Pharmacotherapy

Incomplete improvement is the rule for patients with OCD treated with any therapeutic modality. Nevertheless, symptomatic reductions of 25% (one standard definition of response) or more represent worthwhile gains. Patients in medication multicenter controlled trials typically had a decrease in time spent with obsessions and rituals of at least 2 hours/day.

Patients who do not achieve worthwhile gains may have received treatment of insufficient duration. Experts agree that at least 10 weeks of monotherapy must be completed before concluding that a particular SRI is ineffective. If symptoms prove resistant to an adequate duration trial of the maximum tolerated dose of one potent SRI, a trial of another

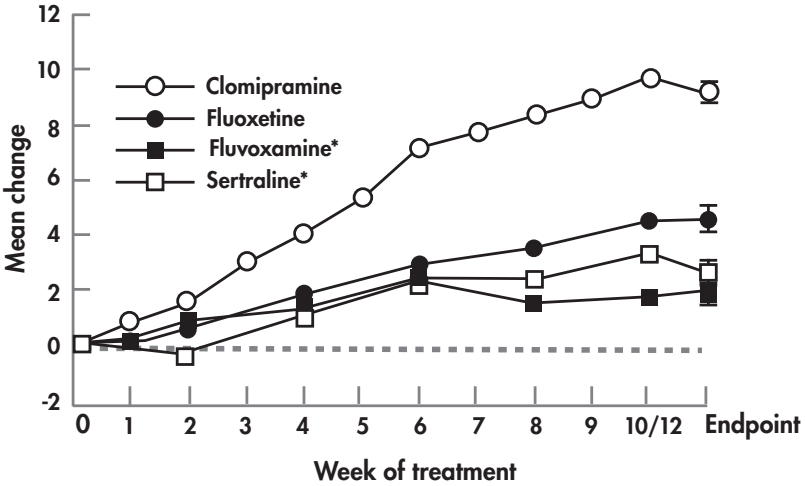

FIGURE 21–2. Mean change in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score: intent-to-treat analysis of drug minus placebo.
Pooled standard error of change score was used in error bars (available for endpoint only).
*12 weeks of treatment for fluvoxamine and sertraline.
Source. Reprinted from Greist JH, Jefferson JW, Kobak KA, et al: "Efficacy and Tolerability of Serotonin Transport Inhibitors in Obsessive-Compulsive Disorder: A Meta-Analysis." *Archives of General Psychiatry* 52:53–60, 1995. Copyright 1995, American Medical Association. Used with permission.

potent SRI is appropriate. Many clinicians believe that higher doses are required in OCD, and such may be the case for select patients, although controlled studies do not support generally higher dosages. One study (Pato et al. 1990) found that virtually all patients who relapsed when clomipramine (275 mg/day) was discontinued responded when retreated at a lower dose (165 mg/day). Essentially flat dose-response curves within a dose range equivalent to 20–80 mg of fluoxetine and 50–200 mg of sertraline were confirmed in multicenter randomized controlled trials.

For patients unresponsive to or intolerant of oral clomipramine, intravenous clomipramine given daily for 2 weeks at dosages increasing from 25 to 200 mg/day sometimes initiates improvement that can be maintained with oral clomipramine (Fallon et al. 1998; Koran et al. 1997). The intravenous advantage may result from lessened effects of first-pass hepatic metabolism, yielding higher ratios of clomipramine to the more noradrenergic desmethylclomipramine. Inhibiting the metabolism of clomipramine with fluvoxamine may be a convenient method for producing "oral-intravenous clomipramine" (Szegedi et al. 1996), though this combination will increase combined blood levels of clomipramine and desmethylclomipramine and warrants blood level monitoring as a guard against seizures and possible cardiac arrhythmias.

SRI Augmentation Strategies

Proserotonergic Strategies

Proserotonergic augmentations have seemed logical in a disorder so clearly responsive to potent SRIs, particularly when there has been a partial response

to a potent SRI. Open-label augmentations with lithium, tryptophan, fenfluramine (no longer available), and buspirone suggested benefit for each proserotonergic augmentation, but controlled trials of lithium (McDougle et al. 1991; Pigott et al. 1991) and buspirone (Grady et al. 1993; McDougle et al. 1993; Pigott et al. 1992) found neither drug significantly more effective than placebo (although some patients did appear to have worthwhile improvement). The combination of clomipramine and citalopram was supported in an open-label randomized trial (Pallanti et al. 1999).

Antipsychotics

Because patients have obsessions and rituals that often seem "crazy," and may seem so at some level to clinicians despite preservation of insight in all but a few cases, it is understandable that antipsychotic medications would be tried for OCD. With the exceptions described below, typical antipsychotics have not been routinely helpful in the treatment of OCD, and because of the common occurrence of extrapyramidal side effects and the risk of tardive dyskinesia, they should not be used without careful thought.

The most promising of augmentation strategies for OCD has been the addition of an antipsychotic drug to a potent SRI (haloperidol plus fluvoxamine and risperidone plus clomipramine, fluoxetine, fluvoxamine, paroxetine, or sertraline are the combinations that have been best studied). A double-blind placebo-controlled trial found that haloperidol (mean dosage 6.2 mg/day) augmented the efficacy of fluvoxamine in patients with OCD and Tourette's disorder or multiple motor tics, producing an 11-point greater reduction in Y-BOCS scores than placebo (McDougle et al. 1994). A subsequent double-blind placebo-controlled trial of risperidone augmentation (mean dosage 2.2 mg/day) of potent SRIs found that 50% of the risperidone patients benefited substantially, with a mean Y-BOCS score reduction of 8.7 points (versus 2.6 points for placebo) (McDougle et al. 2000). Sareen et al. (2004) reported in a review, "In the placebo-controlled trials with haloperidol, risperidone, olanzapine, and quetiapine, a significantly higher response rate (46%–71%) was found for the antipsychotic groups, compared with no response for the placebo groups. Reports of exacerbation of OCD symptoms with the use of atypical antipsychotics were limited to individuals with a primary psychotic disorder" (p. 167). Discontinuation of a beneficial SRI augmentation by an antipsychotic was associated with a relapse rate of 83.3% (Maina et al. 2003).

Recently, a meta-analysis of 12 double-blind, randomized, placebo-controlled trials of SRI augmentation in OCD with "quetiapine (N=5), risperidone (N=3), olanzapine (N=2), aripiprazole (N=1) and haloperidol (N=1) with a total of 394 subjects" (Dold et al. 2013) found efficacy for antipsychotics over placebo "(relative risk=2.10, 95% confidence intervals [CI] 1.16–3.80). Significant efficacy was identifiable only for risperidone, but not for quetiapine and olanzapine. The results regarding aripiprazole and haloperidol were inconsistent. Overall, about one-third of patients with SRI-resistant OCD benefited from an augmentation strategy with antipsychotics" (Dold et al. 2013, p. 557). In clinical practice, given the risks of antipsychotic medications, the comparatively small benefit likely, and the loss of benefit when antipsychotics effective in OCD are discontinued, trials with antipsychotics with clear efficacy targets and plans for discontinuation when targets are not met are appropriate (Dold et al. 2013).

Antianxiety Agents

Benzodiazepines

Although case reports and some case series suggested efficacy for alprazolam, bromazepam, clonazepam, diazepam, and oxazepam, most randomized controlled trials have failed to confirm efficacy for benzodiazepines in OCD. The first controlled trial comparing a benzodiazepine with an effective pharmacological treatment of OCD was a multiple crossover study with 28 subjects conducted by Hewlett et al. (1992). No significant difference in efficacy was found between clomipramine and clonazepam at 6 weeks; however, clonazepam improvement had plateaued by 3 weeks, whereas clomipramine improvement was continuing at 6 weeks and was numerically greater than that for clonazepam (Y-BOCS change scores of 5.8 and 4.5, respectively). Clonazepam was less well tolerated and led to more dropouts because of side effects ($n=5$) than did clomipramine ($n=1$). Because improvement with clomipramine in other studies has continued for at least 10 weeks, 6-week trials are likely too short to establish comparative efficacy of pharmacotherapies for OCD. Other placebo-controlled trials failed to find efficacy for clonazepam monotherapy (Hollander et al. 2003) or augmentation of sertraline by clonazepam (Crockett et al. 2004).

Azapirones

Buspirone has serotonin 5-HT_{1A} receptor partial agonist effects that are thought to account, in part, for its antianxiety effects. Although Jenike and Baer (1988) found that buspirone was ineffective in an open trial with patients with OCD, Pato et al. (1991) found that buspirone (mean dosage 58 mg/day) was as effective as clomipramine in a small ($N=18$) double-blind trial of only 6 weeks' duration.

Combined Behavioral Therapy and SRI Pharmacotherapy

Adult (Foa et al. 2005) and pediatric (Pediatric OCD Treatment Study [POTS] Team 2004) trials found that behavioral therapy (exposure and ritual prevention for adults and children plus cognitive components for children) reduced severity in Y-BOCS scores more than twice as much as clomipramine in adults and sertraline in children (Figure 21–3). Combining CBT and medication added little benefit to behavioral therapy alone. Relapse after SRI discontinuation is consistently and significantly lower in adults who have also received behavioral therapy (Simpson et al. 2004). Medication treats accompanying or underlying depression and anxiety and may improve compliance with behavioral therapy, which in turn improves the possibility of discontinuing medication without rapid and substantial relapse of OCD.

Other Somatic Treatments

Neurosurgery and Deep Brain Stimulation

For the small minority of patients with OCD who remain most severely ill and incapacitated after adequate trials of behavioral therapy, potent SRIs, and augmentation strategies, consideration of neurosurgical interventions is appropriate.

Modern neurosurgical techniques, involving careful patient selection and stereotactic placement of lesions, are sometimes effective in patients with oth-

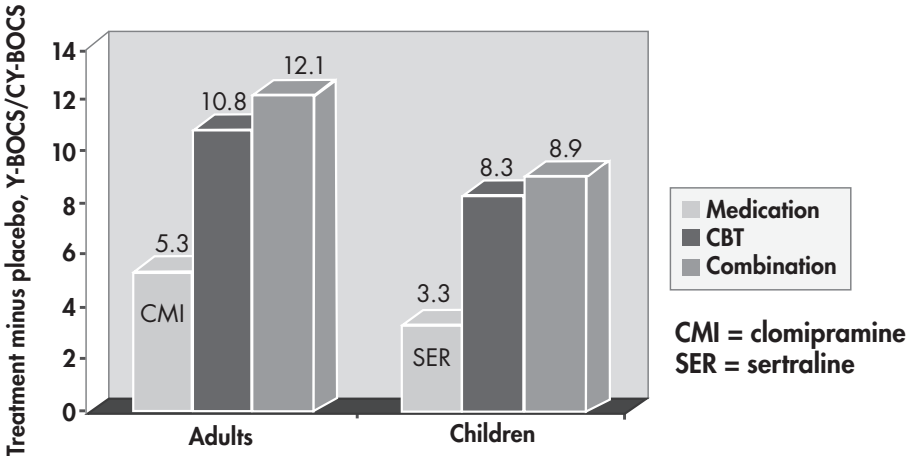

FIGURE 21–3. Efficacy of SRIs and CBT alone and in combination in adult (Foa et al. 2005) and pediatric (Pediatric OCD Treatment Study [POTS] Team 2004) OCD.

erwise refractory OCD and have a low morbidity and virtually no mortality (Baer et al. 1995). Anterior cingulotomy, subcaudate tractotomy, a combination of the two procedures (called limbic leukotomy), and anterior capsulotomy have all been beneficial. A comprehensive review (Greenberg et al. 2003) of modern neurosurgical procedures found that "Existing data suggest that lesion procedures offer benefit to a large proportion (ranging from about 35% to 70%) of patients with intractable OCD and depression" (Greenberg et al. 2003, p. 209).

Emphasis is shifting now to reversible deep brain stimulation in the same areas where irreversible lesions are made (Abelson et al. 2005; Denys et al. 2010; Greenberg et al. 2010). Results have been promising enough that in 2009 the FDA approved a deep brain stimulator for severe, chronic, treatment-resistant adult OCD under its Humanitarian Device Exemption Program.

Promising Treatments Requiring Further Study

Inositol is a second-messenger precursor available in health food stores. In crossover designs, inositol was significantly more effective than placebo as monotherapy for OCD (Fux et al. 1996), but it was not effective as an augmentation for potent SRIs (Fux et al. 1999).

Opiates given every 4–7 days and opiate antagonists prescribed daily have been reported to help some patients with OCD and OCD spectrum impulse control disorders (Koran et al. 2005a; Shapira et al. 1997; Warneke 1997).

Mirtazapine appeared beneficial in both 12-week open-label and subsequent 8-week double-blind placebo-controlled responder discontinuation trials (Koran et al. 2005b).

A randomized controlled trial comparing amphetamine and caffeine augmentation of SRIs in partial responders

produced 48% and 55% reductions in Y-BOCS scores, respectively, at 5 weeks (Koran et al. 2009).

An open trial of SRI augmentation in severe OCD with riluzole, a glutamate antagonist, yielded a mean Y-BOCS reduction of 42% (Coric et al. 2005). Small double-blind placebo-controlled SRI augmentation trials of granisetron, a 5-HT_3 receptor antagonist (Askari et al. 2012), and lamotrigine (Bruno et al. 2012) showed promise.

A single-blind case control study found some benefit of memantine augmentation (Stewart et al. 2010).

Guidelines for Treatment

Behavioral therapy and potent SRIs are the cornerstones of effective treatment of OCD. Evidence strongly supports the conclusion that behavioral therapy is more efficacious than medications, both acutely and in the long term. Behavioral therapy's limited availability is its greatest limitation. If both modalities are available, patients may choose to begin with one or the other, but combined treatment from the outset is also appropriate because one cannot predict beforehand which treatment may be most helpful for a particular patient.

Most patients obtain some benefit from potent SRIs; however, more patients obtain greater benefit from behavioral therapy than from SRIs. Although complete remission is unusual, patients complying with both therapies have a high probability of significant gains (approximately 50% reduction in obsessions and rituals). Patients who have typically suffered for a decade or more both feel and function much better and are quite appreciative of such improvements.

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CHAPTER 22

Body Dysmorphic Disorder

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Body dysmorphic disorder (BDD) is a common (lifetime prevalence of about 2%; Buhlmann et al. 2010) and often severe disorder whose core feature is preoccupation with one or more nonexistent or slight defects in one's physical appearance. The preoccupation causes clinically significant distress or impairment in psychosocial functioning, and it is not better explained by concerns with body fat or weight in an individual who meets diagnostic criteria for an eating disorder (American Psychiatric Association 2013) (see Box 22–1). Insight regarding the perceived flaws (e.g., "I look ugly") is usually absent or poor; most individuals are completely or mostly convinced that their view of their perceived deformities is accurate (Phillips et al. 2012). All persons with BDD, at some point during the illness, perform compulsive behaviors aimed at checking, fixing, hiding, or obtaining reassurance about the perceived appearance defects (Phillips et al. 2005a).

BDD is characterized by poor psychosocial functioning and high rates of suicidality (Buhlmann et al. 2010; Phillips et al. 2005b, 2008; Veale et al. 1996a), yet BDD usually goes undiagnosed in clinical settings (Conroy et al. 2008; Grant et al. 2001).

Box 22–1. DSM-5 Diagnostic Criteria for Body Dysmorphic Disorder

300.7 (F45.22)

A. Preoccupation with one or more perceived defects or flaws in physical appearance that are not observable or appear slight to others.
B. At some point during the course of the disorder, the individual has performed repetitive behaviors (e.g., mirror checking, excessive grooming, skin picking, reassurance seeking) or mental acts (e.g., comparing his or her appearance with that of others) in response to the appearance concerns.
C. The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The appearance preoccupation is not better explained by concerns with body fat or weight in an individual whose symptoms meet diagnostic criteria for an eating disorder.

Specify if:

With muscle dysmorphia: The individual is preoccupied with the idea that his or her body build is too small or insufficiently muscular. This specifier is used even if the individual is preoccupied with other body areas, which is often the case.

Specify if:

Indicate degree of insight regarding body dysmorphic disorder beliefs (e.g., "I look ugly" or "I look deformed").

With good or fair insight: The individual recognizes that the body dysmorphic disorder beliefs are definitely or probably not true or that they may or may not be true.

With poor insight: The individual thinks that the body dysmorphic disorder beliefs are probably true.

With absent insight/delusional beliefs: The individual is completely convinced that the body dysmorphic disorder beliefs are true.

Believing that they look ugly or abnormal, many patients seek and receive cosmetic treatment. Studies from psychiatry settings have found that about two-thirds of patients with BDD receive surgery or dermatological, dental, or other cosmetic treatment for their perceived flaws (Crerand et al. 2005; Phillips et al. 2001a). In one study (N=250), only 7% of such treatments led to overall improvement in BDD (Phillips et al. 2001a), and in another study (N=200), only 4% of procedures improved overall BDD symptoms (Crerand et al. 2005). These outcome data are retrospective but concur with data from a small prospective study (Tignol et al. 2007). In a survey of cosmetic surgeons, 40% reported that a patient with BDD had threatened them legally or physically (Sarwer 2002). Such reports underscore the critical importance of diagnosing BDD and implementing psychiatric treatment.

Before beginning treatment, it is important to lay essential groundwork, with the goal of engaging patients, establishing a therapeutic alliance, and instilling hope. Because most patients have poor or absent insight, they may doubt that they have BDD and that psychiatric treatment can help. Psychoeducation about BDD should be provided, including the fact that it is a common and treatable disorder. Patients may benefit from reading about BDD (e.g., Phillips 2009). Trying to convince or reassure patients with poor or absent insight that they look normal is usually ineffective (one cannot impose insight), and patients typically misinterpret comments about their appearance, even if positive or reassuring, in a negative way. On the other hand, it is important not to agree with patients' negative view of their appearance because this may be devastating to them. It is helpful to empathize with patients' feelings and to focus on the likelihood that psychiatric treatment will improve their distress, preoccupation, and functioning.

Serotonin Reuptake Inhibitors as First-Line Pharmacotherapy

No medications are U.S. Food and Drug Administration–approved for treatment of BDD. However, serotonin reuptake inhibitors (SRIs) are currently considered medications of choice, including for pa-

tients with delusional BDD beliefs (Ipser et al. 2009; National Collaborating Centre for Mental Health 2006; Phillips 2009, 2010; Phillips and Hollander 2008). This recommendation is based on evidence from two controlled studies, four open-label trials, and clinical series.

Serotonin Reuptake Inhibitors as the Medication of Choice for BDD

All published studies indicate that SRIs are efficacious for BDD (Phillips 2010; Phillips and Hollander 2008). In a randomized double-blind crossover study of clomipramine versus desipramine, 29 randomly assigned subjects were treated for 8 weeks with each medication (Hollander et al. 1999). Clomipramine was superior to desipramine for BDD symptoms and functional disability. Treatment efficacy was independent of the presence or severity of comorbid depression, obsessive-compulsive disorder, or social anxiety disorder. This study suggests that SRIs are more efficacious for BDD than non-SRI antidepressants, consistent with retrospective data (see below).

In a 12-week double-blind parallel group study of 67 randomly assigned subjects, fluoxetine was significantly more efficacious than placebo for BDD symptoms and psychosocial functioning (Phillips et al. 2002). The response rate to fluoxetine was 53% versus 18% to placebo. Efficacy in this study, too, was independent of the presence of comorbid major depression or obsessive-compulsive disorder.

In a post hoc analysis, fluoxetine exerted a protective effect against worsening of suicidality compared with placebo (Phillips and Kelly 2009). Four open-label SRI studies have supported efficacy of fluvoxamine, citalopram, and escitalopram (N=15–30) (Perugi et al 1996; Phillips 2006; Phillips and Najjar 2003; Phillips et al. 1998). Similarly, in a clinical series of 33 children and adolescents with BDD, 53% of 19 subjects who received an SRI had improvement in BDD, whereas non-SRI medications were not efficacious for BDD (Albertini and Phillips 1999).

Patients with delusional BDD beliefs often respond to SRI monotherapy (Phillips 2010; Phillips and Hollander 2008). In the previously noted placebo-controlled fluoxetine study, 50% of patients with delusional BDD responded to fluoxetine versus 55% of patients with nondelusional BDD (Phillips et al. 2002). In the previously noted crossover study, clomipramine was even more efficacious for patients with delusional BDD (Hollander et al. 1999). Most studies have found that insight (delusionality) improves with SRI monotherapy (Hollander et al. 1999; Phillips 2006; Phillips and Najjar 2003; Phillips et al. 1998).

The relative efficacy of different SRI doses has not been examined in prospective dose-finding studies. However, available data suggest that BDD often requires higher SRI doses than those typically used for depression (Phillips 2009; Phillips et al. 2001b). Some patients benefit from doses that exceed the maximum recommended dose, but this approach is not advised for clomipramine or citalopram. The average time to response has ranged from 4 to 9 weeks across studies. However, even with fairly rapid SRI dose titration, many patients do not respond until the 10th or 12th week of treatment (Phillips et al. 2002). If SRI response is inadequate after 12–16 weeks of treatment, including treatment at a high dose if necessary for 2–3 weeks, clinical experience

suggests that the medication be changed. Because relapse rates appear high with SRI discontinuation (Phillips et al. 2001b), it is generally recommended that patients who improve with an SRI remain on it for at least several years, although many patients continue an SRI for far longer.

Switching to Another SRI or Augmenting a Partial SRI Response

Partial response to an SRI is more common than remission (Phillips 2009); an SRI typically improves BDD symptom severity by approximately 35%–55% (which corresponds to at least "much improved" on the Clinical Global Impressions scale). Preliminary data suggest that about 40% of initial SRI responders further improve with continued SRI treatment for 6 additional months (Phillips 2009). Alternatively, clinicians can switch to another SRI. A report from a clinical practice found that of those patients who did not respond to an initial adequate SRI trial, 43% responded to at least one subsequent adequate SRI trial (Phillips et al. 2001b).

However, for partial SRI responders, it may be desirable to continue the SRI and augment it with another medication (Phillips et al. 2001b). Buspirone appears to be a good first option; in a chart review study, at a mean dosage of 57±15 mg/day, buspirone effectively augmented SRIs in 33% (N=12) of trials, with a large effect size (Phillips et al. 2001b). The only controlled SRI augmentation study reported that pimozide was not more efficacious than placebo (response rate of 18% to both pimozide and placebo) (Phillips 2005a). A small case series similarly suggested that olanzapine augmentation of SRIs was not efficacious for BDD (Phillips 2005b). However, clinical experience suggests that adding an atypical antipsychotic can be helpful for associated agitation and severe anxiety and perhaps when BDD beliefs are delusional or prominent BDD-related delusions of reference are present.

Data from chart review studies and/or clinical experience suggest that patients may occasionally improve with augmentation of an SRI with bupropion, lithium, methylphenidate, or venlafaxine (Phillips 2009; Phillips et al. 2001a). (Clomipramine levels must be closely monitored, given the SSRIs' potential to substantially raise its level and cause toxicity.)

Adding a benzodiazepine to an SRI should be considered for patients who are very distressed, agitated, or anxious and for whom benzodiazepines are not contraindicated.

Other Somatic Treatments as Monotherapy

Data on non-SRIs as monotherapy are very limited. Small preliminary open-label trials have suggested efficacy for venlafaxine and the anticonvulsant levetiracetam (Allen et al. 2008; Phillips and Menard 2009). In a retrospective case series, monoamine oxidase inhibitors were effective in 30% of 23 cases (Phillips et al. 1994). Tricyclic antidepressants other than clomipramine appear to be inefficacious (Hollander et al. 1994, 1999; Phillips et al. 1994). Retrospective data suggest that antipsychotics do not appear to be effective when used alone to treat BDD (Phillips et al. 1994), despite the high proportion of patients with BDD who have delusional beliefs. On the basis of a small case series, electroconvul-

sive therapy appears to usually be ineffective (Phillips 2009).

Cognitive-Behavioral Therapy

Unlike for SRIs, adequately controlled studies of cognitive-behavioral therapy (CBT) for BDD have not been published. Nonetheless, CBT is the best-studied psychotherapy for BDD, and available data indicate that CBT that is specifically tailored to BDD's unique symptoms may be helpful for a majority of patients (Ipser et al. 2009; National Collaborating Centre for Mental Health 2006; Phillips 2009).

Several case series of CBT in individual or group formats yielded good results (McKay 1999; Neziroglu and Yaryura-Tobias 1993; Wilhelm et al. 1999). More recently, a study of 12 adults that used a manualized individual treatment delivered in weekly individual sessions over 18 or 22 weeks found improvement in BDD and related symptoms (Wilhelm et al. 2011). Treatment gains were maintained at 3- and 6-month follow-up, and patients found the treatment highly acceptable.

Three studies used a wait-list control. A study that provided 8 weekly 2-hour sessions of group CBT found that BDD-focused CBT was efficacious for 77% of 27 women; subjects in the CBT group improved more than those in the no-treatment wait-list control group (Rosen et al. 1995). In a pilot study of 19 patients, those treated with individual BDD-focused CBT improved significantly more than those on a no-treatment wait list, with 7 of 9 CBT-treated patients no longer meeting diagnostic criteria for BDD (Veale et al. 1996b). In another study, 36 adults with BDD were randomly assigned to receive 22 sessions of immediate individual manualized CBT for BDD over 24 weeks or to a 12-week wait list. By week 12, 50% of participants receiving immediate CBT achieved response versus 12% of wait-listed participants ($p=.026$). By posttreatment, 81% of all participants (immediate CBT plus wait-listed patients who were subsequently treated with CBT) were treatment responders, with gains maintained at both 3- and 6-month follow-up. Depression, insight, and disability also significantly improved, and patient satisfaction was high (Wilhelm et al., in press).

Components of Cognitive-Behavioral Therapy for BDD

CBT needs to be tailored specifically to BDD's unique symptoms. Therapists must first provide psychoeducation and build an individualized cognitive-behavioral model of the patient's illness. Motivation may need to be enhanced, and treatment goals that involve enhancement of valued life activities must be set. Recommended treatment then focuses on the following core elements (Wilhelm et al. 2013):

Cognitive restructuring helps patients learn to identify and evaluate their negative appearance-related thoughts and beliefs and to identify cognitive errors (e.g., all-or-nothing thinking, mind reading). Patients learn to develop more accurate and helpful appearance-related beliefs. Core beliefs (e.g., being unlovable, worthless, or inadequate) need to be addressed with more advanced cognitive techniques.

Response (ritual) prevention helps patients cut down on compulsive behaviors (e.g., mirror checking).

Exposure combined with behavioral experiments helps patients gradually face avoided situations (usually social situa-

tions). Exposure is usually combined with behavioral experiments in which patients design and carry out experiments to test the accuracy of their beliefs (e.g., going into a bookstore to test the hypothesis that 70% of people within 3 feet of the patient will move away from the patient within 5 seconds).

Perceptual retraining, which includes mindfulness skills, addresses patients' overfocus on tiny details of their appearance. This approach helps patients learn to look at their entire face or body (not just disliked areas) while looking in the mirror without performing BDD rituals and to objectively (rather than negatively) describe their body. "Mirror exposure," in which patients stare at their perceived defects, is not recommended because this approach may reinforce the ritual of mirror checking and anxiety does not usually appear to habituate.

Relapse prevention at the end of treatment prepares patients to terminate therapy sessions and to continue to implement learned strategies in their daily lives.

Structured daily homework is a necessary treatment component that enables patients to practice and consolidate learned skills.

Additional approaches are recommended for symptoms that some patients have (Wilhelm et al. 2013): 1) *habit reversal* for BDD-related skin picking, hair plucking (e.g., to remove "excessive" body hair), and body touching; 2) *activity scheduling* and *scheduling pleasant activities* for more severely ill, depressed, and inactive patients; 3) focus on *cosmetic treatment seeking;* 4) focus on *body shape or weight concerns*, such as the muscle dysmorphia form of BDD (preoccupation with "small" body build or "insufficient" muscularity); and 5) *motivational interviewing* for patients who are ambivalent about beginning or staying in treatment.

The number of treatment sessions in published studies has varied considerably, from 12 weekly sessions (Veale et al. 1996b) to 12 weeks of daily 90-minute sessions (Neziroglu and Yaryura-Tobias 1993). The optimal session frequency and treatment duration are unclear. Most experts recommend weekly or more frequent sessions for about 6 months plus daily homework. More severely ill patients may require longer or more intensive treatment. Booster sessions following treatment should be considered to reduce the risk of relapse.

Other Types of Psychotherapy

Non-CBT psychotherapy has not been well studied; such studies are greatly needed. There is currently no published evidence that non-CBT therapy improves core BDD symptoms; however, in the author's experience supportive or insight-oriented psychotherapy may be helpful for other disorders or problems the patient may have. On the basis of current knowledge, it is recommended that such treatment be combined with an SRI and/or BDD-focused CBT.

Conclusion

SRIs and BDD-focused CBT are currently the first-line recommended treatments, but additional treatment research is urgently needed, including well-controlled CBT and other psychotherapy studies; augmentation studies of SRIs and CBT; and continuation, maintenance, and relapse prevention studies. There is a particularly pressing need to develop and test treatments for more highly suicidal patients and for children and adolescents.

Recommended Readings

Phillips KA: Understanding Body Dysmorphic Disorder: An Essential Guide. New York, Oxford University Press, 2009

Wilhelm S, Phillips KA, Steketee G: Cognitive-Behavioral Therapy for Body Dysmorphic Disorder: A Modular Treatment Manual. New York, Guilford, 2013

Useful Web Sites

Body Dysmorphic Disorder Clinic & Research Unit: www.massgeneral.org/bdd

Body Dysmorphic Disorder Program at Rhode Island Hospital: www.BDDProgram.com (www.rhodeislandhospital.org/psychiatry/body-image-program)

International OCD Foundation: www.ocfoundation.org

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CHAPTER 23

Hoarding Disorder, Trichotillomania (Hair-Pulling Disorder), and Excoriation (Skin-Picking) Disorder

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Hoarding disorder, trichotillomania (hair-pulling disorder), and excoriation (skin-picking) disorder have long been recognized by clinicians as diagnostic entities. Trichotillomania was included in DSM-III-R (American Psychiatric Association 1987), and hoarding disorder and excoriation disorder are new entities in DSM-5 (DSM-5 criteria for these disorders are shown in Boxes 23–1, 23–2, and 23–3) (American Psychiatric Association 2013). In this chapter, we review the pharmacotherapy and psychotherapy of these disorders.

Box 23–1. DSM-5 Diagnostic Criteria for Hoarding Disorder

300.3 (F42)

A. Persistent difficulty discarding or parting with possessions, regardless of their actual value.
B. This difficulty is due to a perceived need to save the items and to distress associated with discarding them.
C. The difficulty discarding possessions results in the accumulation of possessions that congest and clutter active living areas and substantially compromises their intended use. If living areas are uncluttered, it is only because of the interventions of third parties (e.g., family members, cleaners, authorities).

D. The hoarding causes clinically significant distress or impairment in social, occupational, or other important areas of functioning (including maintaining a safe environment for self and others).
E. The hoarding is not attributable to another medical condition (e.g., brain injury, cerebrovascular disease, Prader-Willi syndrome).
F. The hoarding is not better explained by the symptoms of another mental disorder (e.g., obsessions in obsessive-compulsive disorder, decreased energy in major depressive disorder, delusions in schizophrenia or another psychotic disorder, cognitive deficits in major neurocognitive disorder, restricted interests in autism spectrum disorder).

Specify if:

With excessive acquisition: If difficulty discarding possessions is accompanied by excessive acquisition of items that are not needed or for which there is no available space.

Specify if:

With good or fair insight: The individual recognizes that hoarding-related beliefs and behaviors (pertaining to difficulty discarding items, clutter, or excessive acquisition) are problematic.

With poor insight: The individual is mostly convinced that hoarding-related beliefs and behaviors (pertaining to difficulty discarding items, clutter, or excessive acquisition) are not problematic despite evidence to the contrary.

With absent insight/delusional beliefs: The individual is completely convinced that hoarding-related beliefs and behaviors (pertaining to difficulty discarding items, clutter, or excessive acquisition) are not problematic despite evidence to the contrary.

Box 23–2. DSM-5 Diagnostic Criteria for Trichotillomania (Hair-Pulling Disorder)

312.39 (F63.3)

A. Recurrent pulling out of one's hair, resulting in hair loss.
B. Repeated attempts to decrease or stop hair pulling.
C. The hair pulling causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The hair pulling or hair loss is not attributable to another medical condition (e.g., a dermatological condition).
E. The hair pulling is not better explained by the symptoms of another mental disorder (e.g., attempts to improve a perceived defect or flaw in appearance in body dysmorphic disorder).

Box 23–3. DSM-5 Diagnostic Criteria for Excoriation (Skin-Picking) Disorder

698.4 (L98.1)

A. Recurrent skin picking resulting in skin lesions.
B. Repeated attempts to decrease or stop skin picking.
C. The skin picking causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The skin picking is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., scabies).

E. The skin picking is not better explained by symptoms of another mental disorder (e.g., delusions or tactile hallucinations in a psychotic disorder, attempts to improve a perceived defect or flaw in appearance in body dysmorphic disorder, stereotypies in stereotypic movement disorder, or intention to harm oneself in nonsuicidal self-injury).

Hoarding Disorder

Hoarding disorder is characterized by a persistent difficulty discarding or parting with one's possessions (driven by a perceived need to save the items and by distress associated with discarding them). This results in the accumulation of possessions that clutter living areas and in functional impairment (Mataix-Cols et al. 2010). The community prevalence of hoarding disorder has been estimated to be about 4%–5.8% (e.g., Samuels et al. 2008).

Pharmacotherapy

Because DSM-IV-TR stipulated that in cases of severe hoarding a diagnosis of obsessive-compulsive disorder (OCD) should be considered (American Psychiatric Association 2000), individuals with hoarding symptoms were included in OCD trials of clomipramine (a serotonergic tricyclic antidepressant) and the selective serotonin reuptake inhibitors (SSRIs). There is some evidence that in OCD, hoarding symptoms in particular may respond less robustly to SSRIs (e.g., Grisham and Norberg 2010). One explanation for this finding may be that neurotransmitters other than serotonin (e.g., dopamine) are involved in the pathogenesis of hoarding. These data are, however, based on secondary analyses of patients with multiple symptom dimensions rather than on targeted treatment trials for individuals with primary hoarding. Saxena et al. (2007) specifically assessed response of individuals with hoarding symptoms likely consistent with DSM-5 hoarding disorder (Saxena et al. 2007). Treatment response to paroxetine (mean dose 41.6 mg/day, mean duration 80.4 days) was assessed in 79 patients, 32 of whom had compulsive hoarding symptoms and 47 of whom had OCD. Those with compulsive hoarding responded as well to treatment as did their nonhoarding counterparts. The use of cognitive enhancers and stimulants in the treatment of hoarding disorder has been proposed but not yet systematically studied (Grisham and Norberg 2010). Indeed, in the absence of any controlled trials on DSM-5 hoarding disorder, no specific pharmacotherapy can be recommended strongly at present. Given the literature on SSRIs for hoarding symptoms in OCD and some open-label evidence that these agents are effective in some individuals with compulsive hoarding, an SSRI trial is reasonable.

Psychotherapy

Early psychotherapy trials also recruited individuals with OCD (with or without hoarding symptoms) rather than focusing on those with primary hoarding disorder (Grisham and Norberg 2010). Similar to the pharmacotherapy findings, many of these studies found that within OCD, hoarding was a negative prognostic indicator (e.g., Abramowitz et al. 2003). In response to these findings, a more specific psychotherapy approach to target hoarding symptoms has recently been developed and investigated. This approach is based on a cognitive-behavioral model (Frost and Hartl 1996) that posits that the essential clinical features are due to dysfunctional beliefs and in-

formation processing and avoidant behaviors.

Studies of cognitive-behavioral therapy (CBT) for hoarding disorder have been undertaken. In an uncontrolled trial of 14 adults, 26 individual sessions of CBT with frequent home visits over a 7–12 month period led to a significant improvement (Tolin et al. 2007). In a randomized controlled trial versus wait list in 46 patients, Steketee and colleagues (2010) found that multicomponent CBT (a combination of motivational interviewing and skills training, e.g., problem solving and organizing) and more standard CBT techniques such as psychoeducation, exposure to situations of discarding items, and response prevention (i.e., restricted acquisition of items) over 12–26 sessions yielded significant improvement. There is also preliminary evidence of feasibility and efficacy of group CBT in individuals with hoarding disorder. For example, in a preliminary uncontrolled trial of 32 individuals divided into five groups, Muroff and colleagues (2009) found that 16–20 weekly 2-hour sessions resulted in significant improvement.

Trichotillomania (Hair-Pulling Disorder)

Trichotillomania (TTM) is characterized by recurrent pulling out of one's hair, resulting in hair loss, and repeated attempts to decrease or stop this hair pulling. TTM is thought to affect 0.6%–3.4% of the adult population and has a female preponderance (e.g., Woods et al. 2006a). Neuroimaging studies partially support the hypothesis that the neurobiology of OCD and TTM are distinct but at the same time show some overlap (Lee et al. 2010; Rauch et al. 2007). The three interventions that have been most rigorously investigated for TTM are the SSRIs, clomipramine, and habit reversal therapy (HRT). Meta-analysis of seven randomized controlled trials indicates that although HRT is more efficacious than both pharmacotherapeutic agents, clomipramine is superior to SSRIs in TTM (Bloch et al. 2007).

Pharmacotherapy

Selective Serotonin Reuptake Inhibitors

Fluoxetine has been the most rigorously investigated SSRI for the treatment of TTM (Bloch et al. 2007). Although early open trials and case series of this SSRI showed promise (e.g., Koran et al. 1992), more recent controlled trials have been disappointing. For example, in two randomized controlled trials of 6–12 weeks, fluoxetine outcome did not significantly differ from placebo (Christenson et al. 1991; Streichenwein and Thornby 1995). Furthermore, in a recent wait-list controlled study of fluoxetine versus behavioral therapy (BT) for TTM, fluoxetine was less effective than BT (van Minnen et al. 2003).

Tricyclic Antidepressants

In a double-blind crossover trial, Swedo and colleagues (1989) found that 5 weeks of treatment with clomipramine (mean dose 180.8 mg) was superior to treatment with desipramine (mean dose 173.1 mg). In a randomized controlled trial, Ninan and colleagues (2000) found that clomipramine was not significantly superior to placebo, but this agent was numerically superior and the trial was underpowered. The unfavorable side-effect profile of clomipramine relative to the selective serotonin reuptake inhibitors may, however, limit its utility as a first-line monotherapy (Franklin et al. 2011).

Atypical Antipsychotics

An emerging body of evidence suggests that antipsychotic agents may be helpful for individuals with TTM, particularly those with treatment-resistant symptoms. Early case reports focused on using antipsychotics to augment serotonin reuptake inhibitors. More recent case studies have suggested possible efficacy of aripiprazole (Jefferys and Burrows 2008) and quetiapine (Khouzam et al. 2002) monotherapy. A small 12-week, randomized, double-blind, placebo-controlled trial of olanzapine for TTM (Van Ameringen et al. 2010) found that 11 of the 13 participants (85%) in the olanzapine group showed significant response to treatment (mean dose 10.8 mg/day) compared with only 2 of the 12 (17%) in the placebo group. Given the known side effect burden of antipsychotics, additional studies are needed to determine their role in the treatment of TTM.

Miscellaneous Medications

In one open-label pilot study, Lochner and colleagues (2006) examined the safety and efficacy of the anticonvulsant topiramate in the treatment of TTM. Although results were promising, with a significant decrease in severity of hair pulling, placebo-controlled studies are required to confirm these findings. The mood-stabilizing anticonvulsants lamotrigine (Moretti 2008) and oxcarbazepine (Leombruni and Gastaldi 2010) have also shown some promising preliminary data in open-label studies of TTM, but controlled trials are needed.

There has been recent interest in nutraceuticals such as inositol and *N*-acetylcysteine in TTM. Although inositol appears promising in preliminary open-label work, there are no randomized controlled trials (Seedat et al. 2001). In one randomized controlled trial of the glutamatergic agent *N*-acetylcysteine, a 12-week course (1,200–2,400 mg/day) was significantly more efficacious (56% response rate) than placebo (16% response rate), with no adverse events (Grant et al. 2009). Thus, *N*-acetylcysteine holds promise for the treatment of TTM, and studies comparing its efficacy to SSRIs, clomipramine, and/or psychotherapeutic interventions are warranted (Franklin et al. 2011).

Psychotherapy

Habit Reversal Therapy

Among psychotherapeutic interventions for TTM, HRT has demonstrated the greatest efficacy, with effect sizes superior to pharmacotherapeutic agents (Bloch et al. 2007). HRT is a cognitive-behavioral approach that consists of awareness training (in which the individual is made aware of the preceding urge and act of hair pulling), stimulus control (including measures to decrease or prevent hair pulling), stimulus-response or competing response intervention (in which individuals are encouraged to engage in substitute activities if the urge to hair pull occurs), and self-monitoring (Bloch et al. 2007). Randomized controlled trials and expert consensus guidelines support the use of CBT (in particular, HRT) as first-line therapy for individuals with TTM (Bloch et al. 2007; Chamberlain et al. 2009; Flessner et al. 2010). However, further work is needed to understand fully which components of HRT are most useful and for whom. Some work has evaluated the efficacy of HRT combined with acceptance and commitment therapy (ACT), an emerging cognitive-behavioral strategy that encourages acceptance of inevitable adverse experiences and promotes active commitment to adaptive strategies. In a randomized controlled trial of combined ACT and HRT, Woods and colleagues (2006b) found that individuals in the treatment

group (n=12) demonstrated significantly greater symptom and impairment reduction than those in the wait-list control (n=13).

Group Cognitive-Behavioral Therapy

Group CBT for TTM did not show sustained efficacy in a single randomized controlled trial comparing it with a supportive therapy group (Diefenbach et al. 2005). In the CBT group, individuals were managed with HRT as well as relaxation training, psychoeducation, self-motivation, and relapse prevention techniques. Although the CBT group showed a significant improvement in TTM symptoms immediately posttreatment, these gains were not maintained at 1-, 3- and 6-month follow-up.

Combined Pharmacotherapy and Psychotherapy

In one double-blind randomized medication augmentation study (Dougherty et al. 2006), individuals who had responded poorly to initial sertraline (or placebo) monotherapy were assigned add-on HRT. At study completion, individuals receiving sertraline and HRT showed significantly greater treatment gains than those being treated with sertraline alone. However, given the small sample size (and high rates of attrition), replication studies are required to support this finding.

Excoriation (Skin-Picking) Disorder

Excoriation disorder is characterized by recurrent skin picking resulting in skin lesions as well as repeated attempts to stop or decrease the skin picking. This disorder is thought to affect between 1.4% and 5.4% of the general population (Grant and Odlaug 2009; Grant et al. 2012), and it is a chronic and often disabling condition. Although onset of symptoms may occur at any age, most individuals present clinically during adolescence, with the head and face most commonly affected (Grant and Odlaug 2009). A small literature on the neurobiology of skin-picking disorder (Grant et al. 2012) suggests that there may again be partial overlap in the mechanisms responsible for OCD, TTM, and excoriation disorder, with a particularly strong overlap between the psychobiology of TTM and excoriation disorder.

Pharmacotherapy

Selective Serotonin Reuptake Inhibitors

SSRIs are the most extensively investigated pharmacotherapeutic agents for the treatment of excoriation disorder. In the first placebo-controlled trial, Simeon and colleagues (1997) found that a 10-week course of fluoxetine (mean dose 55 mg/day) was associated with a significant improvement in two out of three outcome measures. This finding was supported in a subsequent small study (Bloch et al. 2001) in which half of the study sample (n=8) responded to initial open-label fluoxetine treatment, and four of these responders maintained clinically significant symptom improvement when randomly assigned to double-blind fluoxetine (whereas the four responders randomly assigned to the placebo group did not maintain their initial treatment gains).

Escitalopram (Keuthen et al. 2007) and fluvoxamine (Arnold et al. 1999) have also appeared useful in two separate open-label trials. Whereas these prelimi-

nary findings show promise, there is clearly a need for controlled studies with larger samples.

Glutamatergic Agents

One open-label study of a 12-week course of lamotrigine (up to 300 mg/day) resulted in symptom improvement in 16 of 24 patients (Grant et al. 2007); however, a subsequent double-blind placebo-controlled trial did not replicate this finding (Grant et al. 2010). Several case reports suggest the therapeutic potential of other modulators of the glutamatergic system. For example, a 4-week course of *N*-acetylcysteine (increased to 1,800 mg/day) resulted in near-complete remission of skin-picking urge and behavior in a 39-year-old woman (Odlaug and Grant 2007). Similarly, Sasso and colleagues (2006) reported the case of a 52-year-old woman with comorbid OCD, major depression, and anorexia nervosa who experienced global improvement in response to riluzole (100 mg twice daily) added to fluoxetine.

Opioid Antagonists

In light of evidence that endogenous opioid hyperactivity may contribute to self-injurious behavior (Winchel and Stanley 1991), the long-acting opioid receptor antagonist naltrexone has been hypothesized to be useful in individuals with excoriation disorder (Herman et al. 1987; Barrett et al. 1989). Although controlled trials support the value of naltrexone in self-injurious behavior, further work is required before it can be recommended for skin-picking disorder.

Psychotherapy

HRT has also been studied for excoriation disorder. Teng and colleagues (2006) found that participants randomly assigned to the HRT group showed greater symptom reduction at posttreatment and 3-month follow-up than did their waitlisted counterparts. In a preliminary investigation of a deliberately limited version of ACT, Twohig and colleagues (2006) reported symptom improvement in a small sample of individuals. However, treatment gains were not maintained at follow-up, thus suggesting that a more extensive program might be necessary for these individuals. Another recent pilot study investigated the efficacy of acceptance-enhanced behavior therapy (AEBT) for excoriation disorder and TTM (Flessner et al. 2008). This approach combines standard HRT with ACT (Yovel 2009). Flessner and colleagues (2008) found that AEBT greatly reduced skin-picking behavior in all five study participants. Additional studies with larger samples and more rigorous methodology would be useful in exploring this combined psychotherapeutic approach further. Internet-based self-help groups for TTM and excoriation disorder have also shown promise in preliminary uncontrolled studies (Flessner et al. 2007). This therapeutic modality has potential to provide widespread access to affected individuals without the need for specialist care. However, there are no controlled data to date.

Conclusion

Despite growing evidence of the prevalence and impact of obsessive-compulsive and related disorders, there are relatively few randomized controlled trials, and no pharmacological agents have received U.S. Food and Drug Administration approval for use in these disorders (Grant and Potenza 2004). Although research has grown in recent years, studies often are limited by small sample sizes, methodological biases, and limited follow-up (Grant and Potenza 2004). Larger controlled treatment trials are needed to

strengthen the empirical database. In the interim, management decisions should be individualized and may incorporate both pharmacological and psychotherapeutic strategies. The SSRIs remain a useful consideration in hoarding disorder, TTM, and excoriation disorder, and there is growing interest in the use of *N*-acetylcysteine in TTM and excoriation disorder. CBT treatments have been adapted for hoarding disorder, TTM, and excoriation disorder, and early evidence suggests that they may be useful for the treatment of these conditions, although trials against controls other than wait list need to be undertaken.

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PART V

Dissociative Disorders and Trauma- and Stressor-Related Disorders

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There have been some important changes in the dissociative disorders diagnostic class from DSM-IV to DSM-5 that affect treatment as well as diagnosis. The definition of dissociative identity disorder has been altered to emphasize the intrusive nature of the dissociative symptoms as disruptions in consciousness, including an experience of possession as an alteration of identity, and to specify, also, that amnesia for everyday, as well as traumatic, events is typical. Dissociative fugue has been included as a specifier of dissociative amnesia, so it is no longer a separate diagnosis. Derealization has been added to depersonalization disorder. Dissociative symptoms are among those in acute stress disorder but are not required for the diagnosis. Finally, a dissociative subtype has been added to posttraumatic stress disorder (PTSD), which, along with acute stress disorder, has been moved from the anxiety disorders to the trauma- and stressor-related disorders. For this subtype to be applicable, all of the DSM-5 PTSD symptoms must be present, in addition to depersonalization or derealization. There is evidence that individuals with these dissociative symptoms benefit from psychotherapies that emphasize stabilization, mood regulation, and relapse prevention, in addition to working through trauma-related memories.

Effective treatment of the trauma- and stressor-related disorders involves a primary focus on psychotherapy, with adjunctive use of medication for symptom control and treatment of comorbid disorders such as depression and anxiety. These are disorders of consciousness, often initially interrupted by stress and trauma. Salient psychotherapy includes attention to stabilization, emotion regulation, stress management, working through of traumatic experiences, and consolidation of treatment gains. Psychiatry has focused on disrupted cognition (schizophrenia) and mood (depression,

bipolar disorder) but has paid less attention to intrusions into and gaps in consciousness, such as those that occur in dissociative identity disorder and dissociative amnesia. Abnormalities in mind-body and perceptual awareness, as in depersonalization/derealization disorder, are common during the acute experience of trauma and become problems in themselves for some over long periods of time. Dissociation calls for reintegration, with an emphasis on acknowledging, bearing, and putting into perspective stressors that contribute to the fragmentation of identity, memory, and consciousness.

The role of dissociation in acute stress disorder and in PTSD, as reflected by the new dissociative subtype in that disorder, highlights the role of dissociation both in regulating strong emotional response to trauma and in suppressing such reactions to the point that treatments that would be expected to work, such as prolonged exposure, may instead trigger further dissociation and prevent access to and working through of trauma-related memories. Recent neuroimaging research has demonstrated that dissociation involves frontal hyperactivity coupled with limbic inhibition, the opposite of what is seen in the hyperarousal types of PTSD. Furthermore, those individuals prone to such dissociative responses to trauma are more likely to have a history of early childhood trauma and abuse. Thus, the treatments described in this part call for training in emotion regulation, cognitive restructuring, and danger avoidance, in addition to exposure-based working through of traumatic memories.

There are no specific medications to treat these problems, though antidepressants, mood stabilizers, and antianxiety medications may play an adjunctive role, especially in treating comorbid disorders such as depression and anxiety. Dissociation is a failure of integration, so the treatments for it must integrate emotion, cognition, memory, and somatic control. The authors of the chapters that follow, all experts in dissociative and adjustment disorders, bring considerable experience in assessment and treatment, an empirical orientation to evaluating outcome, and a willingness to combine specific psychotherapies with psychopharmacology. Dissociation demands integration.

CHAPTER 24

Dissociative Identity Disorder

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In DSM-5 (American Psychiatric Association 2013) dissociative identity disorder (DID) is described as a disruption of identity characterized by two or more distinct personality states or an experience of possession (see Box 24–1). The clinician may observe or the patient may report that these personality states demonstrate marked discontinuity in sense of self and/or agency, accompanied by changes in affect, behavior, consciousness, memory, perception, cognition, and/or sensory-motor functioning. In addition, the person experiences dissociative amnesia (DA), a disruption in autobiographical memory (see Chapter 26, "Dissociative Amnesia") that includes gaps or difficulties in recall of everyday events, important personal information, and/or traumatic events (Loewenstein 1991).

Box 24–1. DSM-5 Diagnostic Criteria for Dissociative Identity Disorder

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A. Disruption of identity characterized by two or more distinct personality states, which may be described in some cultures as an experience of possession. The disruption in identity involves marked discontinuity in sense of self and sense of agency, accompanied by related alterations in affect, behavior, consciousness, memory, perception, cognition, and/or sensory-motor functioning. These signs and symptoms may be observed by others or reported by the individual.

B. Recurrent gaps in the recall of everyday events, important personal information, and/or traumatic events that are inconsistent with ordinary forgetting.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The disturbance is not a normal part of a broadly accepted cultural or religious practice. **Note:** In children, the symptoms are not better explained by imaginary playmates or other fantasy play.
E. The symptoms are not attributable to the physiological effects of a substance (e.g., blackouts or chaotic behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

In recent years, the evidence base has become increasingly rigorous for the current Phasic Trauma Treatment Model for DID described in this chapter (Brand et al. 2012). However, despite DID's being a relatively common psychiatric disorder in the general population, many clinicians have limited education about DID and its treatment. Accordingly, we begin this chapter with some basic information about DID to frame the later discussion of treatment. For a more complete discussion of treatment of DID and related conditions, the reader is referred to several comprehensive reviews (Courtois and Ford 2009; International Society for the Study of Dissociation 2011; Loewenstein and Welzant 2010).

Population studies in North America, Europe, and Turkey have found that DID is a relatively common psychiatric disorder, occurring in about 1%–3% of the general population and up to approximately 20% of patients in inpatient and outpatient treatment programs (Spiegel et al. 2011). A causal relationship between antecedent trauma and dissociation has been validated across cultures in clinical and nonclinical samples using a variety of methodologies (see Dalenberg et al. 2012). Individuals with DID show the highest rates of early life trauma compared with all other clinical groups (Spiegel et al. 2011). Individuals with DID report multiple forms of early maltreatment, usually emotional, physical, and/or sexual abuse, as well as neglect, beginning before the age of 5, although nonmaltreatment early life trauma, such as multiple painful early life medical procedures, has also been reported (Putnam 1997). Also, individuals with DID report high rates of adult traumatization, such as rape, intimate partner violence, and being sexually trafficked (Simeon and Loewenstein 2009).

DID is conceptualized as a childhood-onset posttraumatic developmental disorder in which the traumatized child is unable to complete the normal developmental processes involved in consolidating a core sense of identity. Instead, repeated early trauma disrupts unification of identity through creation of discrete behavioral states that encapsulate and provide relief from traumatic experiences. Often accompanied by disturbed caretaker-child attachment and parenting, repeated early trauma disrupts the development of normal metacognitive processes involved in the consolidation of a unified sense of self across different contexts, for example, with parents, peers, and others (Freyd 1996; Lyons-Ruth et al. 2006; Ogawa et al. 1997; Putnam 1997). Over time, these self-states may become subjectively personified and begin to develop along different developmental trajectories. With adolescence, further elaboration of these self-states may occur, leading to the phenomenology associated with adult forms of DID (Loewenstein and Putnam 2004).

Definitions

Dissociation as an Adaptive Response to Trauma or Overwhelming Circumstances

Dissociation can be understood in dimensional and adaptive terms with patients with DID, not just in categorical, psychopathological ones. Early dissociation represents an adaptive response to inescapable threat and/or danger, where fight or flight is impossible or may lead to even greater harm and where comforting and restorative experiences are unavailable, other than what the child develops to comfort himself or herself (Kluft 2001; van der Hart et al. 2006). The traumatized child retreats inwardly because no other escape is possible from overwhelming events and related unendurable affective states (Kluft and Loewenstein 2007).

Studies show that early childhood dissociation can also be a resiliency factor in DID, in which psychological sequestration of trauma memory appears to allow some aspects of normal development to occur (Brand et al. 2009a). When compared on psychometric measures with patients with borderline personality and psychotic disorders, patients with DID show significantly greater psychological complexity; capacity for insight, reality testing, and logical thinking; and preserved sense of humor, creativity, and hopefulness and even the belief that relationships can be positive and cooperative, although these strengths can be overwhelmed when the person is destabilized or triggered by traumatic material. These capacities may underlie the responsivity of individuals with DID to specialized treatment, despite their symptoms, deficits, and impairments.

Complex Posttraumatic Stress Disorder

Most individuals with DID fit the model of complex posttraumatic stress disorder (CPTSD). CPTSD is a construct based on the observation that repeated severe traumatic events, primarily interpersonal trauma across developmental epochs, result in a set of characteristic deficits in multiple domains of functioning (Courtois and Ford 2009; Herman 1992). These deficits include difficulties with affective regulation, difficulties with regulation of consciousness (e.g., liability to dissociation and state changes), difficulties with sense of self and body image (e.g., identity problems, eating disorders, lack of attention to medical needs, and somatization), relationships with intense mistrust coexisting with vulnerability to victimization and exploitation, deformations in systems of meaning (e.g., the world seen as dangerous and the self as damaged and responsible for traumatization), and self-destructiveness (including suicide attempts, self-injury, substance abuse, and risk-taking behaviors).

Dissociative Subtype of Posttraumatic Stress Disorder

A related body of research has led to the characterization of a dissociative subtype of posttraumatic stress disorder (DPTSD), a diagnostic construct that is included in the DSM-5 diagnostic criteria for posttraumatic stress disorder (PTSD; see Chapter 27, "Posttraumatic Stress Disorder") (Lanius et al. 2010, 2012; Stein et al. 2013). Depending on the study, approximately 15%–30% of PTSD patients will fit this subtype of PTSD. Compared with nondissociative PTSD patients, DPTSD individuals usually report multiple epi-

sodes of childhood maltreatment or trauma. In addition, when hearing their own personal trauma scripts, DPTSD patients report depersonalization, derealization, and other dissociative symptoms; concomitantly display neural networks characterized by activation of frontal circuits that appear to have a dampening effect on emotional limbic structures such as the amygdala and insula; and frequently show reduced or no change in blood pressure and heart rate.

Indeed, in an imaging study using trauma scripts with patients with DID, the traumatic identity state responded to the script as a personal autobiographical memory with fear and activation of the amygdala, insula, and related neural and autonomic systems; a decrease in perfusion of the frontal cortex; and autonomic activation. Conversely, the neutral identity state experienced personal trauma scripts as if they were nonautobiographical memories and showed activated frontal systems that appeared to have a suppressing effect on emotional, limbic regions, as well as dampened autonomic responses (Reinders et al. 2006).

Comorbidities in Patients With DID

Large-population studies have shown that early life trauma and maltreatment are correlated in stepwise fashion with increasingly high rates of depression, substance abuse, suicidality, self-destructiveness, problems with relationships, work impairment, revictimization, a number of DSM-IV-TR diagnoses, amnesia for early life, and hearing voices, among others (Felitti and Anda 2010). Many high-risk behaviors and major medical problems are associated in stepwise fashion with increasing levels of exposure to early adversity, including morbid obesity; high-risk sexual behavior; risk of sexually transmitted diseases; early pregnancy; autoimmune disease; and serious cardiac, hepatic, and pulmonary problems (Felitti and Anda 2010). DID represents the most extreme end of the childhood trauma continuum, so it is not surprising that high rates of these types of comorbidities are commonly found in patients with DID and require clinical attention.

Treatment Outcome Studies

Complex and Dissociative Forms of PTSD

Convergent data from treatment outcome studies of CPTSD, DPTSD, and DID patients have shown lack of response or even clinical deterioration if standard, unmodified progressive exposure or cognitive-behavioral treatment models for PTSD are used with these populations (Cloitre et al. 2010; D'Andrea and Pole 2012; International Society for the Study of Dissociation 2011). Treatment paradigms that do not use exposure or use exposure only in highly modified protocols after a period of stabilization of dissociation and other CPTSD symptoms have been developed and have proven effective for individuals with DPTSD (Cloitre et al. 2012; Resick et al. 2012).

Dissociative Identity Disorder

Meta-analytic Findings

Brand et al. (2009c) performed a meta-analysis of eight outcome studies for dissociative disorders, including inpatient

and outpatient settings and treatment by nonexpert and expert clinicians. Despite the methodological limitations of these studies, the phasic model of DID treatment was associated with improvements across a range of symptoms and comorbidities. These improvements included reductions in diagnoses of comorbid Axis I and II disorders as well as improved dissociation, depression, anxiety, suicidality, and substance abuse and decreased general distress. In studies from an inpatient specialty trauma disorder program, gains persisted at 2-year follow-up. Effect sizes based on within-patient preassessments and postassessments were in the medium to large range.

TOP DD Study

Studies using prospective naturalistic designs can ethically evaluate treatment outcome in populations with severe symptoms that do not readily allow for short-term, manualized psychotherapy studies. Such a design was used in the study Treatment of Patients with Dissociative Disorders (TOP DD), which prospectively assessed outcomes from 280 patients with DID or dissociative disorder not otherwise specified and 292 therapists from 19 countries at 4 time points over 30 months of treatment (Brand et al. 2009b, 2012; Towson University College of Liberal Arts 2013). Therapists indicated which of five treatment stages—using subdivisions in the tri-phasic model—best characterized their patients in the previous 6 months of treatment.

The cross-sectional TOP DD results showed that patients in the first stage of treatment had higher levels of dissociation, PTSD, and overall distress; more hospitalizations; and less adaptive functioning than patients in the last stage of treatment. As reported by patients and therapists, at 30-month follow-up, patients showed decreased dissociation, PTSD, general distress, depression, suicide attempts, self-harm, dangerous behaviors, drug use, physical pain, and hospitalizations, as well as improved functioning and higher Global Assessment of Functioning scores (Brand et al. 2012). More patients were involved in volunteer jobs and/or attending school and socializing and reported feeling good. Furthermore, more patients progressed from early stages of treatment to more advanced stages than regressed from an advanced to early treatment stage (Brand et al. 2012).

Indeed, even the TOP DD patients with the highest levels of dissociation, as well as those with the most severe depression, showed significant improvements in these symptoms over 30 months (Engelberg and Brand, 2012; Brand and Stadnik 2013). Younger patients stabilized self-injurious behaviors and suicide attempts more rapidly than older patients, suggesting that early diagnosis and appropriate treatment are important (Myrick et al. 2012). Rates of revictimization showed a trend toward reduction over the course of the study (Myrick et al. 2013). More patients showed "sudden improvement" than "sudden worsening" (i.e., 20% increase or decrease in symptoms) at one or more time point(s) (Myrick et al. 2013). Therapists reported fewer revictimization events and stressors among the sudden improvers compared with those who worsened, suggesting that revictimization and/or stressors may have contributed to worsening in treatment. Worsening over more than one data collection point occurred in only a very small minority (1.1%) of the patients. This rate compares favorably to the 5%–10% of psychiatric patients who show worsening symptoms during treatment in general (Hansen et al. 2002).

In summary, the TOP DD study documented that with appropriate DID treatment, a wide range of symptoms and adaptive functioning improve and utilization of higher levels of care decreases. The consistency of this pattern across a breadth of outcome variables, corroborated by data from both therapists and patients, strongly suggests that treatment contributed to the improvements.

Norwegian Inpatient Treatment Study

A Norwegian study of consecutive admissions to an inpatient trauma program found that dissociation does not substantially improve if amnesia and dissociated self-states are not directly addressed (Jepsen et al. 2013a). Female inpatients with childhood sexual abuse (CSA) without a DD were compared with a CSA group diagnosed with a DD (DID or DDNOS). None of the patients diagnosed with a DD had previously been assessed or treated for a DD, nor was their DID directly treated while they were hospitalized; thus, this study's methods reduce the possibility that therapists or treatment may have suggested features of DD. One year prior to hospitalization, a baseline assessment showed that patients' dissociative symptoms were stable and severe prior to treatment, thus reducing the possibility that the passage of time or regression to the mean contributed to improvements. Although both groups reported some dissociative symptoms, the DD group was more symptomatic across all measures, including dissociation. Both groups showed statistically significant decreases in symptoms associated with treatment, including dissociation, although the effect sizes for change in dissociation were smaller for the DD group than for the non-DD group (d=.25 and 69, respectively). An interaction between dissociation and worsening in interpersonal functioning prior to treatment predicted poor outcome at follow-up (Jepsen et al. 2013b). These results led the treatment team to create specialized treatment for DD patients, the evaluation of which is underway (E. Jepsen, personal communication, June, 2013). Thus, across studies of trauma patients, provision of dissociation-specific treatment is often associated with better outcome (Cloitre et al. 2012).

Phasic Treatment

Brand et al. (2013) reported on a comprehensive survey of 36 international DID experts to identify evidence-based interventions for treatment of DID. Their recommendations, the ISSTD Treatment Guidelines (International Society for the Study of Trauma and Dissociation 2011), and the interventions documented in the TOP DD study form the basis for the treatment recommendations that follow. The experts rated the frequency of 28 recommended interventions in treatment of patients with DID across five stages of treatment (stage 1: safety and stabilization; stage 3: processing trauma and grieving; stage 5: integration, fusion, and reconnection) (Brand et al. 2013). Frequency of endorsements ranged from 0 (never) to 4 (very often). The top 10 most frequently recommended interventions for each treatment stage are shown in Figure 24–1.

Overview

In the first stage, the patient works toward basic safety and stability. In the third stage, the focus is on the detailed narrative and emotionally intense recollection and processing of trauma memories, although many patients may not have the practical or psychological resources for

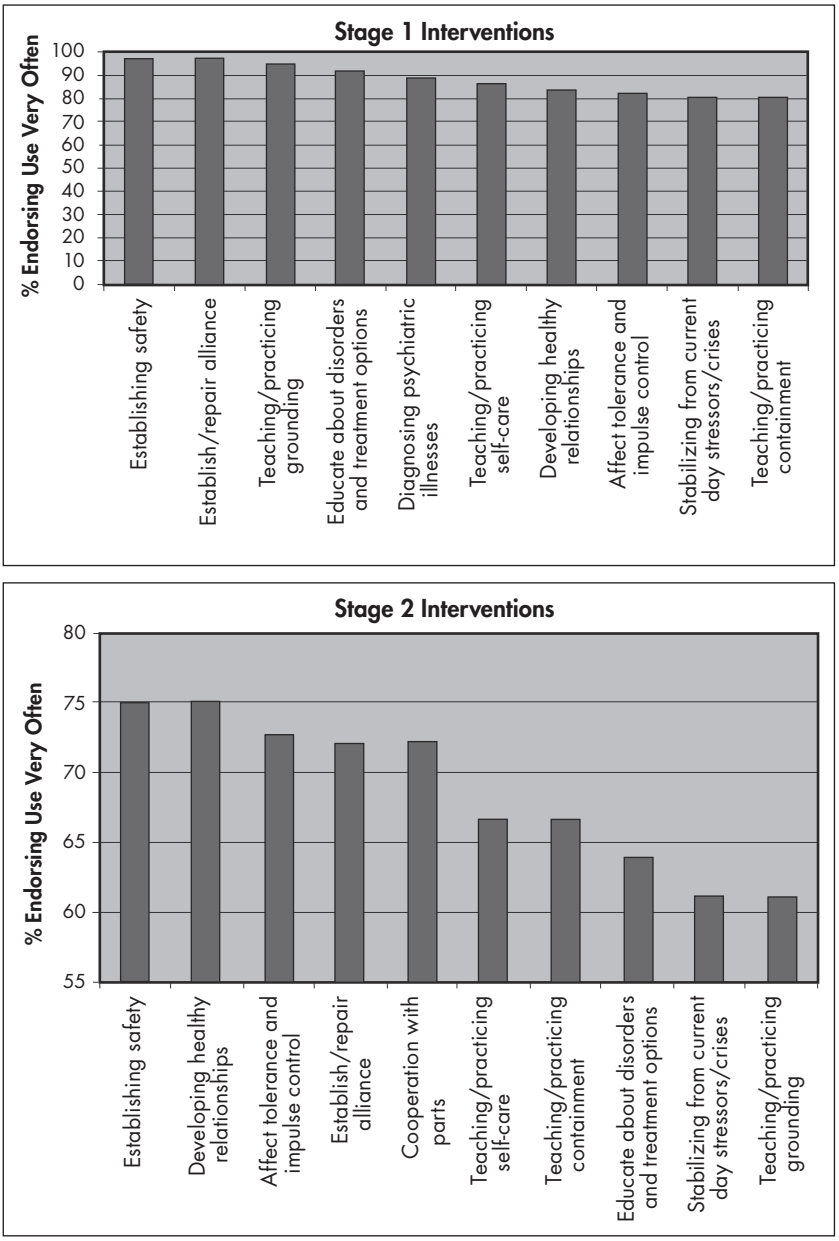
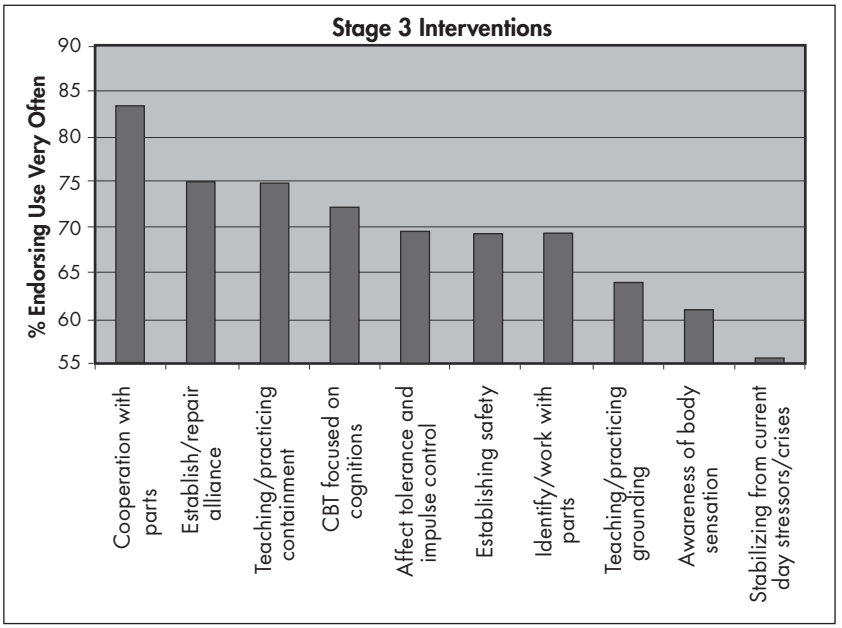


FIGURE 24–1. Top 10 interventions by stage.

Source. Brand BL, Myrick AC, Loewenstein RJ et al: "A Survey of Practices and Recommended Treatment Interventions Among Expert Therapists Treating Patients With Dissociative Identity Disorder and Dissociative Disorder Not Otherwise Specified. *Psychological Trauma: Theory, Research, Practice, and Policy* 4:490–500, 2012. Used with permission.



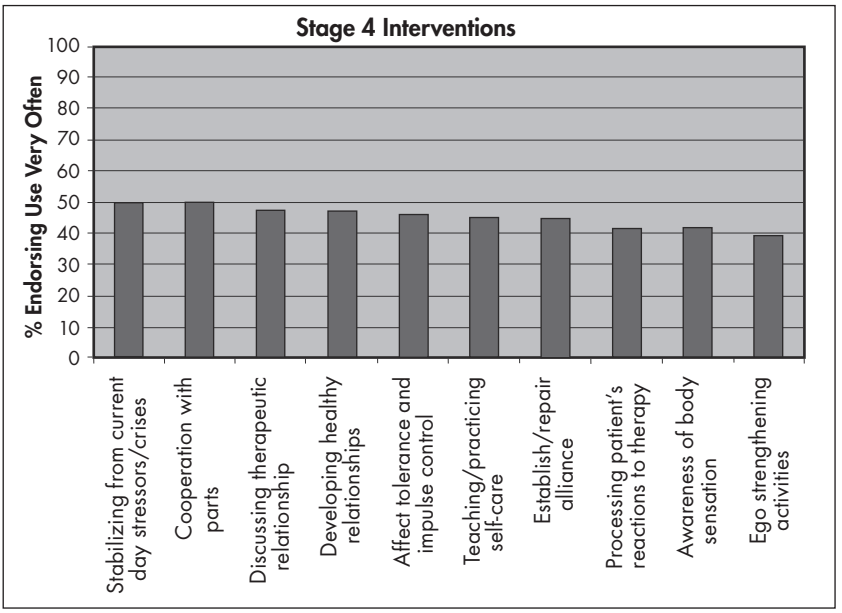


FIGURE 24–1. Top 10 interventions by stage *(continued).*

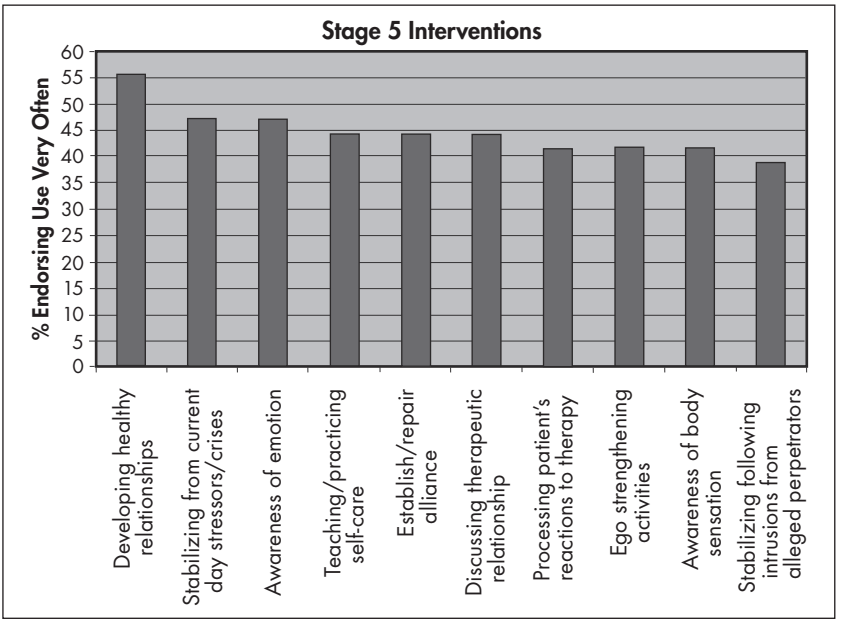


FIGURE 24–1. Top 10 interventions by stage *(continued).*

full stage 3 work. In the fifth stage, the therapeutic work is directed toward "reintegration," living well in the present, with traumatic memories relegated more to the status of "bad memories" rather than flashbacks, behavioral reenactments, and/or intense posttraumatic reactivity. These stages are heuristic because memory material may need to be addressed, if only in a cognitive and distanced manner, in stage 1 and worked through again from a more integrated perspective in stage 3. Safety may be an issue at all stages of trauma treatment. The entirety of trauma treatment is directed toward the patient developing a better adaptation to current life (Kluft and Loewenstein 2007; Loewenstein and Welzant 2010).

Core Therapeutic Interventions

Across the stages of treatment, the 36 experts established a core set of techniques helpful for treatment of DID, as well as interventions that are specific to substages (Brand et al. 2013). Developing and repairing the therapeutic alliance was recommended as a top intervention in every stage of treatment, indicating the centrality of the therapeutic alliance in the successful treatment of DID (Kluft 1994). The experts recommended assessing and stabilizing safety as a top 10 intervention in all but the last stage of treatment. Safety continues to be a focus across all stages because each stage can bring about crises or emotions that patients may feel compelled to manage via self-destructive behavior or, less commonly, behavior that endangers others (Myrick et al. 2013). Other core interventions recommended across all stages of treatment include diagnosis and treatment of comorbid psychiatric disorders, providing psychoeducation about disorders and treatment, assessing the adequacy of medication, increasing awareness of emotion, develop-

ing affect tolerance and impulse control, managing daily functioning and current relationships, processing reactions to therapy, and stabilizing patients following stressful life situations and/or intrusions from abusive individuals.

Grounding techniques such as moving, focusing on one's five senses, or touching an object to control "trancing" or dissociating were recommended across all stages to assist with overlap and interference among self-states and switching. Containment of traumatic material was recommended across all but the last stage. Containment techniques may include teaching self-hypnosis and imagery to control the intrusiveness of traumatic material,[1] ego strengthening (i.e., interventions to promote better overall functioning, including calming imagery, reaffirming statements, and relaxation training), specific trauma-focused cognitive work to change trauma-based cognitions (e.g., confusing past and present, self-blame for abuse, and delusions of separateness among self-states[2]), and focusing on safety issues (i.e., discussing the antecedents to and functions of self-destructive and suicidal behavior and aggressive behavior toward others, as well as developing safety agreements and crisis management plans). Given the consistency of the strategies recommended by experts, the authors of the expert survey concluded that these interventions make up the core treatment processes and structure for treating DID. The consistency of the recommendations in the expert survey (Brand et al. 2013) and the ISSTD Treatment Guidelines indicates that a standard of care is emerging for the treatment of DID.

Stage 1: Safety and Stabilization

Work on safety and stability for the patient with DID is the critical first step in treatment—and often the one most neglected. Patients with DID commonly come to treatment because of problems with safety and/or overwhelming symptoms. The types of safety problems encountered in DID include danger to self, including self-destructive behavior and repeated suicide attempts; danger to others, including to the minor children of the patient; eating disorders; substance abuse; high-risk behaviors (e.g., reckless driving); enmeshment in abusive or traumatizing relationships, including with the family of origin; lack of food, clothing, or shelter; and lack of access to and/or avoidance of medical care. While working on safety, the clinician is simultaneously developing the therapeutic alliance; providing educational and cognitive interventions; and teaching skills to manage dissociative, posttraumatic, and affective symptoms (Kluft and Loewenstein 2007).

Expert consensus and evidence-based studies strongly support direct work with dissociative self-states. Treatment that does not involve direct interaction with self-states has poorer outcome overall for patients and/or may cause iatrogenic worsening. Interventions may include identifying self-states, "talking over" the

[1]Hypnosis for DID treatment should be undertaken only by clinicians who have obtained certification in hypnosis and received specialty training in hypnosis for severely traumatized or dissociative individuals.

[2]Delusion of separateness is the belief by self-states that they do not inhabit the same body and/or are unaffected by what happens to other self-states or the person's body (e.g., they will not die if suicide is successful).

presenting self-state to other states that may be "listening," helping develop patterns of inner communication among self-states, and assisting with internal empathy, collaboration, and cooperation among self-states.

The self or personality of the individual with DID is made up of all the self-states, rather than viewing one state as the "real person" (Putnam 1997). All self-states should be treated evenhandedly by the therapist (Kluft 2001). In addition, the clinician should hold the patient with DID responsible for his or her behavior, even when that behavior is disavowed because of dissociative amnesia or lack of subjective control (Loewenstein and Putnam 2004). To do otherwise is an invitation to regression and crises. Therapists can attempt to understand the subjective mental state of the person with DID during problematic behaviors, but empathic understanding does not exculpate the patient from responsibility for behavior across all states (Loewenstein and Putnam 2004). On the other hand, there are no "good" or "bad" self-states; rather, self-states are adaptive responses to aspects of the person's experiences—traumatic or otherwise—and overall development, although this view is not an endorsement of the behaviors that are attributed to specific self-states. Accordingly, clinical deterioration is the usual response of the patient to attempts to ostracize or "get rid of" certain self-states.

Stage 3: Processing Trauma and Grieving

Studies show that at least one-third of DID patients do not stabilize sufficiently or have the desire and/or the psychological, social, or economic resources to engage in the rigorous second stage of treatment. (See Kluft 1997, 2001; Kluft and Loewenstein 2007; and Loewenstein and Welzant 2010 for criteria for readiness for stage 2 work.) Instead, these patients require long-term supportive psychotherapy focused on maintaining reasonably safe and stable functioning. A subgroup of these patients will function at the level of the chronically and persistently mentally ill, whereas others use supportive treatment to maintain occupational and family functioning.

In stage 3 treatment, it is essential to carefully pace and plan trauma-focused work. In-depth exploration of trauma is not done as frequently with dissociative trauma patients because of their vulnerability to destabilization. Prior to discussing traumatic memories in detail, the patient and therapist need to collaboratively decide what material will be worked on, with what intensity of affect, and with which self-states, as well as plan for potential problems that may arise during and after the session (Loewenstein and Welzant 2010). The patient explores trauma-based beliefs, traumatic memories, and trauma-based reenactments. Patients express emotions and physical sensations that have been avoided, including grief, terror, helplessness, betrayal, shame, and rage. Patients are helped to develop coherent narratives of traumatic as well as nontraumatic experiences. As this stage progresses, patients develop a sense of mastery over their memories; gain distance from trauma-related beliefs; and gradually have less intrusive, uncontrolled PTSD symptoms, even changing flashback memories into "ordinary bad memories" without the ineluctable quality of the flashback.

Stage 5: Integration, Fusion, and Reconnection

The term *integration* in DID treatment defines a therapy-long process of amelioration of all forms of dissociative pro-

cesses and defenses. Integration encompasses improved memory continuity, communication, and collaboration among self-states in stage 1, leading to subjective unification of all self-states—with a shift in subjective self from a *multiple* subjective self to a *single* subjective self—in stage 5 and continuing on into *postunification*, treatment in which the patient learns to live and cope without self-states (Kluft 2001).

The term *fusion* is defined as a point in time when two or more self-states subjectively merge all their characteristics, memories, emotions, and senses of self, with a shift in subjective experience to that of a "new" or "changed" self-state, encompassing all the attributes of the previously separate selves (see Kluft 1993). This is a remarkable, yet poorly studied, clinical process that can occur spontaneously or with imagery or hypnotic facilitation by the therapist (Kluft 1993, 2001). Generally, fusions result in an increase in subjective well-being, less trauma-based thinking and reactivity, improved insight, and better self-regulation. Some patients will claim to have *integrated* all self-states without actually having done the staged therapy work to make this possible and without showing the expected commensurate improvements associated with genuine final fusion (see Kluft 1993, 2001 for enumeration of these improvements). Many patients will not achieve a final or stable fusion, defined as demonstrating psychological unification over at least 27 months. Instead, they will maintain what is termed a *resolution* in which some self-states persist but in a more adaptive configuration (Kluft 1993, 2001).

In stage 5, the treatment focus shifts toward greater emphasis on living well in the present, including mastering new coping skills for life without pathological dissociative defenses despite everyday stress. The patient shows improved distress tolerance, affect modulation, and subjective well-being. Accordingly, the patient has greater energy, enthusiasm, and resilience for new relationships, life tasks, and avocations. At the same time, memory material may need to be reworked and additional grief work done to more fully acknowledge the reality of the patient's traumatic life history.

Pathological Possession Trance and DID

The DSM-5 diagnostic criteria for DID include "an experience of possession" as a cultural variant of DID that occurs in non-Western cultures and in some Western subgroups, such as in certain fundamentalist Christian groups (Spiegel et al. 2011). Pathological possession is experienced as different from culturally accepted forms of possession, is usually related to antecedent traumatic or stressful events, and bears significant phenomenological overlap with DID, although the possessing entities are primarily attributed to outside forces (spirits, demons, djinns, mythical figures, gods, etc.). However, many Western patients with DID report either "feeling" or actually believing that they are "possessed," especially if self-states appear to have characteristics that are highly psychologically dissonant (e.g., a self-state based on a former abuser). Western patients may also have self-states based on mythical figures, gods, animals, spirits, and so forth (Spiegel et al. 2011).

Treatment of pathological possession trance does not have the same evidence base as the model described in this chapter. However, there are broad similarities with Western DID treatment, including di-

rect negotiation with the possessing states, allowing them to "give voice" to their concerns, and assisting them with identifying and redressing their problems. As treatment progresses, the possessing personality states may shift to a more adaptive configuration or unify into a subjectively singular self (Spiegel et al. 2011).

Adjunctive Treatment Modalities

Psychopharmacological Treatments and Electroconvulsive Therapy

Detailed review of these topics can be found in the International Society for the Study of Trauma and Dissociation (2011) treatment guidelines and in work by Loewenstein (2005). In brief, there are no known psychopharmacological treatments that target the process of dissociation itself. Somatic treatments are adjunctive to the psychotherapy described above. Psychopharmacological targets should be directed at symptoms found across all or most DID self-states. For example, if one self-state displays the symptoms of major depressive disorder and other states do not, psychopharmacological treatment is unlikely to be efficacious. Common comorbid targets include mood disorder symptoms, PTSD symptoms, self-destructive behaviors, and sleep problems. Symptoms of obsessive-compulsive disorder are common in DID and often respond to antiobsessive medications. Typical medication targets and their treatments are found in Table 24–1.

The psychiatrist should be aware that symptoms in DID and related CPTSD disorders rarely respond definitively to medications, with the exception of prazosin for PTSD nightmares, to which there may be a very robust response (Raskind et al. 2003). In general, medications for these patients should be conceptualized as "shock absorbers," with the goal of the most parsimonious, efficacious, and least problematic medication regimen for the patient at a given time. Patients' symptoms may be exacerbated by stressors and/or difficult work in therapy. Accordingly, rapid changes or major adjustments in medication at these times are likely to be more confusing than helpful.

Patients with DID commonly report inner voices or conversations of self-states and may report visual, tactile, olfactory, gustatory, and somatosensory hallucinations, usually as a manifestation of partial flashbacks. In addition, they commonly report passive influence symptoms due to overlap and interference of self-states. Accordingly, an incorrect diagnosis of a psychotic process is often made and intensive neuroleptic regimens are initiated, at best with minimal response, because DID hallucinations and related phenomena stem from dissociative and posttraumatic factors, not a psychotic illness.

Often in DID, a highly depressed self-state is the cause of sustained mood symptoms that are unresponsive to pharmacological intervention or electroconvulsive therapy (ECT), and these symptoms improve only with psychotherapy to address the depressed state. Expert consensus (International Society for the Study of Trauma and Dissociation 2011) about the use of ECT to treat DID is that it is usually unlikely to be of benefit and may cause significant additional memory problems unless there is a clear-cut, sustained "double depression" clinical picture with persistent symptoms of melancholia across the whole human being that is distinctly different from the patient's usual baseline, chronically depressed mood. Here, ECT

TABLE 24–1. Medication targets and typical response in DID

Mood disorder symptoms: the usual baseline is "depressed all my life"

- Patient shows partial response to SSRIs, SNRIs, buproprion, TCAs, and MAOIs
- There is sporadic, limited response to antidepressant augmentation with mood stabilizers or amphetamines
- There is a lack of response to mood stabilizers for putative bipolar disorder, where the patient has rapid mood or state shifts in minutes to hours, usually related to DID and PTSD
- Response of mood shifts to mood stabilizers may occur when true sustained mania or hypomania is present over at least several days alternating with major depressive symptoms that may differ from baseline chronic depression
- When OCD symptoms are present, mood and OCD symptoms may preferentially respond to antidepressants with antiobsessive efficacy

Posttraumatic stress disorder symptoms

- The most consistently robust response is to prazosin for PTSD nightmares and flashbacks, up to 18 mg daily for women and 25 mg for men, in a single bedtime dose or divided doses, as long as blood pressure remains normal (Raskind et al. 2013)
- There may be a partial response of PTSD symptoms to SSRIs, SNRIs, buproprion, TCAs, and MAOIs
- Intrusive PTSD symptoms may respond to clonidine, which is not likely to affect nightmares; blood pressure effects may preclude using both prazosin and clonidine
- Intrusive symptoms may respond to low doses of atypical neuroleptics and sometimes to typical neuroleptics
- Hyperarousal symptoms may respond to propranolol
- Intrusive symptoms may show sporadic response to antiepileptic mood stabilizers, particularly lamotrigine and carbamazepine; lithium is not effective for this indication
- Benzodiazepines (typically clonazepam and lorazepam) may be prescribed for panic and anxiety symptoms; however, PTSD gives rise to terror, not anxiety, and, at best, partial responses are the rule; tolerance and dependence must be evaluated rigorously
- Hydroxyzine may also be useful for anxiety in DID patients with addiction issues or who cannot tolerate benzodiazepines

Sleep problems: typically a mixed depressive and PTSD sleep disorder with specific phobias of nighttime, sleep, and bed if there has been a history of nocturnal maltreatment

- Prazosin is robustly helpful for nightmares
- Trazodone in varying dosages (50–500 mg nightly) may help with sleep problems
- Low-dose neuroleptics may help with sleep problems
- Low-dose sedating antidepressants such as mirtazapine or TCAs may help with sleep problems
- Benzodiazepines and nonbenzodiazepine sedative hypnotics such as zolpidem may help with sleep problems
- Sedating anticholinergic agents may help with sleep problems

TABLE 24–1. Medication targets and typical response in DID *(continued)*

Self-mutilation or other forms of repetitive self-harm, especially accompanied by a subjective "high"
• Patients report decrease in intensity of self-harm drive with naltrexone in varying dosages (not exceeding 200 mg daily); ablation of "high" with self-harm; uncharacteristically feel pain with self-harm

Note. MAOI=monoamine oxidase inhibitor; OCD=obsessive-compulsive disorder; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.
Source. Adapted from Loewenstein 2005.

usually affects only the double depression symptoms, returning the patient to his or her chronically depressed baseline.

Hypnosis

Hypnosis is not a treatment in itself but rather a set of techniques that are useful adjuncts to furthering clinical goals of treatment. Patients with DID have the highest hypnotizability on standardized scales compared with all other clinical groups and normal controls (International Society for the Study of Trauma and Dissociation 2011). Patients with DID naturalistically display symptoms consistent with deep trance phenomena such as recurrent spontaneous trances, intense enthrallment experiences, multimodal hallucinations, negative hallucinations (not perceiving sensory stimuli in the environment), trance logic (tolerance of logical inconsistency in the hypnotic state), spontaneous age regressions, amnesia, and an eye-roll sign while switching self-states (Loewenstein 1991). Thus, every treatment of DID involves hypnotic phenomena in some way (Kluft and Loewenstein 2007). It is helpful for the clinician treating DID to be trained in hypnosis to recognize these clinical phenomena and to utilize them in DID treatment.

The vast majority of hypnotic interventions in DID are for containment, soothing, calming, and ego strengthening; to help attenuate dissociative and PTSD symptoms; and to facilitate communication and collaboration among self-states (Hammond 1990; Kluft 1989). In terms of stage 3 work on memories, hypnosis is primarily used to attenuate and fractionate the intensity of trauma material, not for *uncovering* or *exploration.* Discussion of issues about the accuracy of trauma memory and the possible generation of confabulated memory with adjunctive hypnotic techniques in DID treatment is beyond the scope of this chapter, and reviews are available (Brown et al. 1998; Dalenberg 2006). The clinician should obtain informed consent from the patient for hypnosis as well as educate the patient that retrieval of memory under hypnotic conditions is no more or less likely to be accurate than memory recalled under any other conditions.

Eye Movement Desensitization and Reprocessing

Eye movement desensitization and reprocessing (EMDR) is currently identified as an effective treatment for PTSD (Bradley et al. 2005). However, EMDR has a significant exposure and free association component and in unmodified form can cause significant harm to patients with DID, particularly early in treatment. One of us

(RJL) has considerable experience with DID patients having adverse outcomes to EMDR. These outcomes have included severe posttraumatic and dissociative crises, suicide attempts, self-destructive behavior, and worsening of PTSD or dissociative and mood disorder symptoms, often resulting in emergency hospitalization, as well as sustained decompensation.

EMDR practitioners who work with patients with DID have provided an appendix to Shapiro's (1995) basic text on EMDR and a section on EMDR for the ISSTD Treatment Guidelines (International Society for the Study of Trauma and Dissociation 2011). They caution that in DID, EMDR should be understood as an optional, adjunctive technique that can sometimes facilitate treatment goals, primarily in stage 3. It has to be modified, as does any exposure treatment, to fit the complexity of the patient with DID. Clinicians using EMDR in this population should receive basic and advanced EMDR training as well as have specialized training in the assessment and phasic treatment of CPTSD and DID.

Hospital Treatment

For a review of treatment of complex trauma and dissociative disorders in a specialty hospital setting, see Loewenstein and Wait (2008). In general hospital settings, expert consensus recommends that the treatment team identify specific goals for a relatively brief inpatient stay aimed at managing the acute problem leading to hospitalization (e.g., stabilization of a suicidal self-state and avoidance of "mission creep"). The focus for the staff should be on specific pragmatic, symptom-based goals, not on debates about belief or disbelief in the patient. The patient should be instructed that he or she will be required to use a single name for all public unit endeavors and should strive to present his or her "inner adult" on the unit. Group therapy, other than strict psychoeducational groups, is often problematic, and the patient with DID should be excused from general unit groups if they become unworkable.

Group Psychotherapy

In general, patients with DID do poorly in heterogeneous psychotherapy groups. Often, patients with DID are initially a focus of fascination or bafflement, but as the group progresses, they usually become a focus of exasperation and ostracism. Patients with DID usually do better in highly structured, homogeneous psychoeducational and symptom management groups in which detailed discussion of traumatic memories is eschewed (International Society for the Study of Trauma and Dissociation 2011).

Family and Marital Therapy

Family and marital therapy with the contemporary family of the patient with DID may be helpful if the patient is not enmeshed in an abusive relationship. DID treatment is a demanding, change-oriented process, and the spouse is usually not prepared for the many changes in his or her partner, including symptom exacerbations, sexual phobias, and posttraumatic responding that may occur temporarily as DID treatment progresses. In particular, the patient's spouse and children should be advised to not interact with the patient as an agglomeration of selves—learning their names, asking for self-states to emerge, and so forth. Rather, the patient should be encouraged to be a parent to his or her children, not a playmate, and to be related to as much as possible as a whole human being.

Cost Savings

Health costs associated with DID are important to consider. Among spouses of military personnel, those with dissociative disorders (DDs) utilized the highest number of outpatient therapy sessions of any of 17 psychiatric disorders studied (Mansfield et al. 2010), although there is no information about whether DD patients were receiving treatment consistent with the ISSTD Treatment Guidelines.

Specialized treatment for DID is associated with significant cost savings (Loewenstein 1994). In Canadian outcome studies for DID, costs were reduced for less chronically ill patients from an average of C$75,000 per year per patient prior to DID diagnosis to an average of C$36,000 per patient per year in the 3 years after correct diagnosis, although in the second and third years of the study, costs were reduced to an average of C$10,600 per patient per year (Ross and Dua 1993). Cost savings were extrapolated for treatment if the patients had continued in incorrect treatment for another decade. These savings ranged from C$1.35 million to C$3.75 million (Loewenstein 1994). These and other studies document specific, dramatic cost savings even for chronically ill DID patients, averaging about $30,000 per year for specific patients who had spent years in the mental health system (Lloyd 2012; Ross and Dua 1993).

Conclusion

The current empirical data strongly suggest that treatment consistent with the standard of care articulated in the expert guidelines for patients with DID is associated with improvement in functioning and a decrease in symptoms in a broad range of domains as assessed by both patients and therapists in case studies, cross-sectional studies, and prospective longitudinal trials. Although randomized clinical trials have not been conducted, current evidence is consistent with the conclusion that DID treatment is responsible for the improvements seen in patients' symptoms and functioning. Given the severe symptomatology, dysfunction, and cost associated with this disorder, treatment that is consistent with expert consensus DID treatment guidelines and current research is strongly indicated for DID patients.

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Useful Web Sites

International Society for the Study of Trauma and Dissociation (ISSTD): www.isst-d.org

International Society for Traumatic Stress Studies (ISTSS): www.istss.org

Trauma Center at Justice Resource Institute: http://www.traumacenter.org/

Trauma Disorders Program at Sheppard Pratt Health System: www.traumaatsp.org

Treatment of Patients With Dissociative Disorders: www.towson.edu/topddstudy/index.asp

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CHAPTER 25

Depersonalization/ Derealization Disorder

Daphne Simeon, M.D.

Initial Evaluation

Depersonalization is the subjective experience of detachment or estrangement from one's own self. Derealization is the equivalent subjective experience as applied to one's surroundings, animate or inanimate. Because the two experiences often, although not always, co-occur and because there is no empirical evidence to support their discrete nature, a single classification has been adopted in DSM-5 (American Psychiatric Association 2013): depersonalization/derealization disorder (DRD; see Box 25–1 for criteria). To merit the diagnosis, a person must be experiencing clinically significant depersonalization and/or derealization (i.e., persistent or recurrent and associated with distress and/or impairment) that is not exclusively due to another psychiatric or medical condition or to ongoing substance use, and reality testing regarding these experiences must be intact. All criteria leading a clinician to make the diagnosis are important to appreciate and assess early on in encounters with new patients because the disorder is commonly misdiagnosed or underdiagnosed. With a prevalence of 1%–2% in several epidemiologic samples (Aderibigbe et al. 2001; Hunter et al. 2004) and significant associated morbidity, a delay in diagnosis and appropriate treatment leads to prolonged suffering (Simeon et al. 2009).

Box 25–1. DSM-5 Diagnostic Criteria for Depersonalization/ Derealization Disorder

300.6 (F48.1)

A. The presence of persistent or recurrent experiences of depersonalization, derealization, or both:

1. **Depersonalization:** Experiences of unreality, detachment, or being an outside observer with respect to one's thoughts, feelings, sensations, body, or actions (e.g.,

perceptual alterations, distorted sense of time, unreal or absent self, emotional and/or physical numbing).

2. **Derealization:** Experiences of unreality or detachment with respect to surroundings (e.g., individuals or objects are experienced as unreal, dreamlike, foggy, lifeless, or visually distorted).

B. During the depersonalization or derealization experiences, reality testing remains intact.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, medication) or another medical condition (e.g., seizures).
E. The disturbance is not better explained by another mental disorder, such as schizophrenia, panic disorder, major depressive disorder, acute stress disorder, posttraumatic stress disorder, or another dissociative disorder.

Several further points are important to note in attaining an accurate diagnosis. Although DSM-5 does not include a criterion for duration of symptoms, most clinicians will apply the diagnosis, if all other criteria are met, for symptoms that have lasted for 1 month at the very least, and definitely for a 3-month duration. Patients experiencing depersonalization often have great difficulty putting their impalpable experiences into words. Furthermore, unfamiliarity with the symptoms and the diagnosis often makes individuals fear that they will be mistaken for "crazy," that they are becoming psychotic, or that they have irreversible brain damage. On the other hand, clinicians typically focus on comorbid symptoms such as mood and anxiety, sometimes to such an extent that the prominent dissociative symptoms are either entirely missed or minimized in the bigger clinical picture. Patients who are ultimately given the diagnosis often report that they were previously diagnosed as suffering from depression, anxiety, or simply some form of "stress." The symptoms, although quite specific, may appear vague or metaphorical to a clinician who has rarely encountered them and who might therefore mistrust his or her clinical judgment and knowledge in applying the diagnosis. Typically, the symptoms are highly distressing, at times crippling, culminating in a subjective state that patients may describe as the "living dead" or "loss of self," and as such are associated with major morbidity and some mortality. The lifeless and robotic demeanor that these patients often demonstrate on initial mental status exam can also fool clinicians into not recognizing the extreme emotional pain of the condition. It is not uncommon for patients to wonder what would be the point of dying because they have already lost their selfhood and so, in a sense, are dead.

There are several symptom domains that need to be inquired about in order to successfully diagnose, as well as fully and empathically appreciate, the scope of the disorder through the patient's own subjective state of mind (Sierra et al. 2005; Simeon et al. 2008). Specific symptoms of these domains should all be inquired about and are summarized in Table 25–1. The broad domains that need to be inquired about include unreality of the self, numbing, perceptual alterations, temporal disintegration, and unreality of surroundings.

Depersonalization disorder may have an episodic relapsing and remitting or a continuous, chronic course (Simeon et al. 2003). The latter is most common, especially over time, characterizing about two-thirds of all patients. Various degrees of impairment in occupational and/or in-

TABLE 25–1. Symptoms of depersonalization/derealization disorder

Unreality of the self
Self feels absent or dead; no self
Detachment from physical body or parts
Detachment from mind or thoughts
Detachment from feelings
Detachment from behaviors or actions (robotic, going through the motions; observing-participating split)
Numbing
Emotional numbing (blunted emotional experience, hypoemotionality)
Physical numbing (decreased sensitivity to touch, physical pain, hunger, thirst, libido)
Perceptual alterations
Visual alterations (sharper, duller, two-dimensional, tunnel-like)
Auditory alterations (heightened or distant sounds, detachment from own voice)
Olfactory and gustatory alterations (blunted, less common)
Temporal disintegration
Time going too quickly or too slowly
Past experienced as remote and disconnected
Difficulty connecting to autobiographical memories, recent and remote
Difficulty evoking visual imagery of one's past experiences
Unreality of surroundings
Dreamlike, foggy, through a veil or glass, surreal, detached from environment

terpersonal functioning occur. Even patients who maintain relatively intact occupational functioning will typically state that they feel cognitively compromised and as if they are not performing at their prior capacity. Interpersonally, some patients become profoundly isolated, but even those who do not will lament the sense of disconnection and seeming loss of feelings for others that they intellectually know they have. Mean age of onset is around adolescence or early adulthood in most cases. Some patients can date their symptoms to a younger age, or as far back as they can recall, and some will describe onset in their thirties. Onset of the disorder in the 40s and 50s is quite rare. The majority of patients are initially treated for anxiety or mood disorder symptoms, so the primary nature of the depersonalization disorder may not be recognized until later on.

The comorbidity frequently associated with depersonalization/derealization can complicate the differential diagnosis of DRD (Baker et al. 2003; Simeon et al. 2003). Many patients have coexisting psychiatric disorders, most commonly mood and anxiety disorders, as well as personality disorders, primarily borderline, obsessive-compulsive, and avoidant. Less commonly, chronic depersonal-

ization may result from a medical or neurological condition or be secondary to substance use effects, so it is therefore essential to conduct a thorough medical and neurological evaluation that includes standard laboratory studies, electroencephalogram (EEG), any indicated drug screens, and brain imaging for any suspicion of lesions. In certain cases of difficult-to-diagnose suspicion of an underlying seizure disorder, an ambulatory EEG may be indicated. In order to establish the psychiatric differential, detailed psychiatric history needs to be obtained. Although lifetime mood and/or anxiety disorders have been reported in up to 90% of DRD patients (Simeon et al. 2003), criterion D requires that the depersonalization/derealization not occur exclusively in the context of these other disorders: it must antedate them, must continue after their resolution, or, if concurrent, must be by history and presently disproportionate to such comorbidities. It is common, for example, to obtain a history whereby a prior episode of anxiety or depressive disorder, which presumably acted as an internal stressor and destabilized a person's known sense of self, precipitated a chronic depersonalization syndrome that continues after the initial anxiety or mood episode remits. In making the differential diagnosis from psychotic spectrum disorders such as schizophrenia, prodromal schizophrenia, or schizotypal personality disorder, it is essential to examine the intactness of reality testing surrounding any perceptual alterations as well as more broadly. The "as if" experiential nature of depersonalization, without distorted cognitive elaborations, is central to the diagnosis.

Self-report questionnaires can also be helpful in confirming the diagnosis of DRD, especially for clinicians who are not as extensively familiar with dissociative symptoms. The very widely used Dissociative Experiences Scale (Bernstein-Carlson and Putnam 1993) has several items pertaining to depersonalization/derealization experiences, and the endorsement of other items pertaining to amnesia and identity alteration should be very low. More specific to the disorder, the Cambridge Depersonalization Scale (Sierra and Berrios 2000) is a self-report questionnaire comprising 29 items that rate both frequency and duration of depersonalization/derealization experiences. A total score of 70 and above has been shown to reliably differentiate DRD patients from those with various mood, anxiety, or neurological disorders.

Initial Interventions

After the diagnosis is definitively reached, treatment options can be implemented. Treatment of all patients with DRD, especially given the fact that DRD is not well known, should incorporate elements of psychoeducation and early supportive psychotherapy. These include the following:

- Information about the nature and course of the disorder, as detailed in the "Initial Evaluation" section above: giving the condition a name can be a significant step for the patient.
- Reassurance about common fears: The condition will not evolve into a psychotic disorder. There is no evidence linking the disorder to permanent brain damage.
- Alleviating potential sources of guilt or shame: In the case of chronic depersonalization triggered by use of an illicit drug, it can be useful to explain to the patient that, while we do not know to a scientific certainty, we assume that the individual had an underlying diathesis for depersonal-

ization, which could have been triggered at any point in his or her life by a variety of chemical or psychosocial stressors. In this respect it is important to know that patients with drug-triggered onset almost invariably become "drug phobic" and stop using. The small minority who continue use should be counseled that they must stop or risk a perpetuation or intensification of symptoms.

- Providing hope for the future: although accurate prognostic statistics based on prospective studies are not available, it is clear that at least a portion of patients, whether with the assistance of treatment or spontaneously, experience improvement or remissions over time.
- Reassuring women who are considering pregnancy: heritability, though not well studied, appears to be limited.
- Challenging the "physicality" of the experience: Emphasize that as physical as the symptoms may feel, the disorder is psychological. This understanding can provide the patient with a sense of control over the symptoms that may otherwise be perceived as continuous in intensity. It may also curtail unnecessary visits and workups with a variety of medical specialists, which are common early on.

Psychotherapies

Several more specific psychotherapies are used to treat DRD, including psychodynamic, cognitive, behavioral, hypnotherapeutic, and supportive therapies. No controlled trials have been performed to assess or compare the efficacy of these interventions. Clinicians working with these patients sometimes have an excessively pessimistic view of treatment responsiveness of depersonalization/derealization symptoms because they often have an opportunity to intervene only years after onset, at which point the symptoms generally tend to become more continuous, constant in intensity, and possibly more resistant to treatment.

Anecdotal evidence strongly suggests that patients are more likely to respond to treatment if it is begun earlier in the course of the disorder, if the disorder has an episodic or fluctuating course, and if the symptoms can be more readily linked to particular cognitive or affective processes. The prognosis can often be better than commonly assumed when one intervenes under these circumstances.

Psychodynamic Psychotherapy

Psychodynamic psychotherapy focuses on underlying threats to self-definition and self-constancy that precipitate affectively intolerable states leading to dissociation (Simeon and Abugel 2006). According to psychoanalytic theory, a person in whom the cohesiveness or stability of self-representations is profoundly threatened may resort to depersonalization, that is, a disconnection from the self, as a response to the overwhelming shifts in self-experience ("it is not me to whom this is happening"). Although a depersonalizing response is to a degree ubiquitous, hardwired, and even adaptive in acute circumstances, its persistence over time becomes maladaptive and pathological. Psychodynamic theory similarly suggests that depersonalization can be linked to all levels of character pathology. In psychotic spectrum character pathology, depersonalization may be triggered by experiences of impaired self and other differentiation. In borderline psychopathology, unstable and switching

self-representations may be associated with depersonalization experiences. In narcissistic pathology, when self-constancy is threatened by loss or failure, real or imagined, of self-objects serving purposes of object constancy, depersonalization may arise. In neurotic-level psychopathology, derepressed self-representations associated with overwhelming intrapsychic conflicts and their associated affects may trigger depersonalization.

In psychodynamic treatment, the therapist has the opportunity to observe and analyze, often in a microprocess, moment-to-moment fashion, such dynamics as they occur inside the session or as they are described by the patient. This microanalysis of depersonalization symptoms as they wax and wane during psychotherapy sessions can be most effectively utilized with an affect phobia psychodynamic model in mind. This model implies that the hypoemotionality, emotional numbness, and alexithymia (inability of individuals with the disorder to describe feelings) stem from a need to "dissociate" unbearable affects and their accompanying cognitions, relational structures, and historical origins.

The goal of an affect-based therapy is to uncover, experience, label, own, and verbalize intolerable emotions and to process such emotions in the context of underlying conflicts and disavowed self-representations and self-states (i.e., poorly integrated components of identity), thus diminishing the psychic pressure to depersonalize. Eventually, such conflictual self-states and their associated overwhelming emotions can be gradually integrated with the core sense of self so that the individual can transition from an "unreal" self to a more "real" owned and known self. The affects needing to be dealt with can vary greatly depending on each person's history and sense of self, ranging from the negative to the positive, and can include anger, grief, sorrow, shame, guilt, excitement, and love. Fundamentally, such a psychodynamic approach counters the defensive aspect of depersonalization/derealization by mobilizing affect rather than detaching from it. This is an approach that is essentially consistent with the treatments of trauma- and stressor-related disorders such as posttraumatic stress disorder or dissociative identity disorder, as the goal in therapy of DRD is to activate and experience, rather than avoid, intense painful affects so as to better temper and regulate them.

At times when patients visibly become, or report, an acute heightening of their depersonalization outside of or inside the treatment, a microanalysis is undertaken in order to determine what the intolerable affects (e.g., anxiety, shame, rage, guilt, excitement, hope) are that are being defended against and the external and internal contexts (cognitions, dynamics, threats to attachment) that have acutely activated the peaking of symptoms. Conversely, when a patient reports moments of lessened depersonalization, in or out of session, the circumstances that facilitated the containment and awareness of difficult affects is explored. No clinical trials have been conducted on psychodynamic psychotherapy for DRD.

In our clinical experience, psychodynamic psychotherapy can be very helpful, especially with patients who have fluctuating symptoms that can be more readily linked to dynamics and who are more psychologically minded. Psychodynamic psychotherapy needs to be conducted at a minimum of once weekly, and often more frequently, so that the intensity and continuity of the treatment become safe yet challenging enough psychically to facilitate breaking through the dissociation and working with the underlying affects and dynamics.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) has been developed and piloted to treat DRD on the basis of a cognitive-behavioral model of the disorder (Hunter et al. 2003). This model postulates that although a variety of external or internal psychological or chemical stressors can trigger the initial symptoms, the disorder is at risk of setting in when there is an initial highly threatening or catastrophic interpretation of the experience, leading to a range of cognitions and behaviors that then perpetuate and intensify the symptoms over time. In cognitive-behavioral therapy based on this model, the focus is on developing techniques with three major goals: reduce symptom monitoring, cognitively reinterpret symptoms as less threatening and overwhelming, and diminish avoidance and safety behaviors.

As an example, consider a patient with DRD who is constantly preoccupied with existential ruminations; has checking rituals to determine whether the symptoms are still present; believes that he or she has suffered irreversible brain damage; and avoids many activities, such as leaving home, socializing, or being in overstimulating environments, out of the fear that these activities will worsen the symptoms. Using thought-blocking and distraction techniques, the patient can be helped to ruminate less and resist checking rituals using a distracting task. Cognitive corrections can be used to counter catastrophic cognitions, such as the one involving irreversible brain damage. A hierarchical exposure approach can be used to help the patient gradually confront, rather than avoid, situations that worsen the symptoms. If anxiety is exacerbating the symptoms, cognitive and relaxation or breathing retraining and grounding techniques involving reorienting the patient to the present time and place can be used to keep anxiety in better check while explaining to the patient the vicious cycle of anxiety triggering more depersonalization and depersonalization then triggering worsened anxiety.

This therapeutic approach is strongly informed by the cognitive-behavioral conceptualization of anxiety disorders and tends to work much better for those patients who have prominent anxiety, ruminations, and obsessive-compulsive-like symptoms surrounding their depersonalization/derealization. It can be useful in patients with any of these characteristics in their presentation; it is otherwise less useful. Limited evidence suggests that CBT may be effective in DRD. An open prospective trial tested CBT with 21 patients (Hunter et al. 2005) and found reductions in depersonalization, derealization, and other psychiatric symptoms after 12 weeks; 29% of participants no longer met criteria for the disorder. Further research on the efficacy of CBT in DRD is needed.

Other Psychotherapy Approaches

Eye movement desensitization and reprocessing (EMDR; Shapiro 1996), a form of CBT that incorporates saccadic eye movements during exposure, has been proposed for use in the treatment of DRD in conjunction with hypnosis, although evidence is very limited (Harriet 2009).

Hypnosis, a state of focused concentration, can be utilized to help patients reconceptualize and control their depersonalization symptoms. Patients are shown how to practice cognitive control over their symptoms through self-hypnosis. They learn how to modulate symp-

toms by making a controlled connection to emotional memories, past self-states, and/or interactions causing different degrees of depersonalization, including pleasant or less threatening forms of depersonalization (Van Dyck and Spinhoven 1997). In our clinical experience, hypnosis can be helpful, at least temporarily, in alleviating symptoms of depersonalization, but there are no data from clinical trials on the efficacy of hypnosis in treating DRD. Three to five sessions are usually sufficient to determine whether or not treatment involving hypnosis is likely to help. A patient's hypnotic capacity can be assessed with the Hypnotic Induction Profile (Spiegel and Spiegel 2004). It appears that some patients with DRD are highly hypnotizable, as is fairly common in other dissociative disorders, whereas others are quite resistant to this modality.

Supportive Psychotherapy

Some more severely impaired patients with DRD may require long-term supportive psychotherapy. These more typically include patients with a chronic, continuous course of unrelenting intensity and minimal fluctuations, limiting the therapist's ability to apply psychodynamic or CBT techniques, and patients whose educational, occupational, or social lives have been profoundly impaired by the disorder. In providing supportive psychotherapy for these patients, the clinician should be acutely aware of the patient's interpersonal sensitivity, profound demoralization and distress, and sense of hopelessness about the condition. The goal of the therapy is to help patients gradually rebuild impaired areas of their lives while coming to greater acceptance of their unchanging symptoms and cultivating some sense of optimism for future treatments.

Pharmacotherapy

There is a lack of robust evidence from randomized trials on the efficacy of medication for DRD, mostly due to the absence of trials rather than negative outcomes. The most commonly used medications in clinical practice to treat the disorder are serotonin reuptake inhibitors, benzodiazepines, lamotrigine, and naltrexone. Other classes of medications are also used on an anecdotal basis. We summarize the available evidence below.

Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) and potent serotonin-reuptake inhibitor (SRI) tricyclics (e.g., clomipramine) are reported to be of some benefit for treating DRD symptoms, especially under certain conditions. They are postulated to reduce comorbid anxiety and depressive symptoms if prominent, which may fuel an intensification of depersonalization symptoms. The only randomized controlled trial for DRD did not find overall efficacy (Simeon et al. 2004). The trial compared fluoxetine to placebo in 50 patients with DRD. Ratings by clinicians and patients did not find clinically significant differences in depersonalization or dissociation change scores between the fluoxetine and placebo-treated groups. However, the subgroup with greater anxiety at baseline that responded to fluoxetine treatment also showed a significant decline in depersonalization symptoms.

An earlier uncontrolled trial reported that two of seven patients with DRD showed improvement following enrollment in an 8-week course of treatment with clomipramine (Simeon et al. 1998). Anecdotally, some patients with DRD whose hypoemotionality worsens with

SSRIs or who suffer from extreme levels of anxiety and obsessionalism appear to have a better response to clomipramine. A retrospective treatment report of patients with DRD (Simeon et al. 2003) found that of 60 patients with DRD treated with an SSRI, 9 patients reported their symptoms had definitely improved, 14 patients reported symptoms were "slightly improved," and 37 reported symptoms "stayed the same or worsened." Of 9 patients with DRD treated with a serotonin-norepinephrine reuptake inhibitor, all of the patients reported that their symptoms stayed the same or worsened. Of 3 patients with DRD treated with clomipramine, all of the patients reported that their symptoms stayed the same or worsened. In our clinical experience, patients with DRD who experience improved anxiety and depression with SRI treatment often report that although the depersonalization itself has not changed, they are less distressed by it and better able to tolerate and ignore it.

Lamotrigine

Lamotrigine, a mood-stabilizing anticonvulsant that promotes glutamate release, has shown fairly positive results in limited studies in DRD, meriting further study. A randomized trial of 80 patients with DRD found that participants treated with lamotrigine were more likely to respond compared with patients receiving placebo, 72% versus 16% (Aliyev and Aliyev 2011). A concern about this study was the generalizability of the patient sample, given the description of enrolled patients as "without psychiatric comorbidity," which is unusual in this population. Two prior small trials came to conflicting findings. Whereas four of four patients with DRD experienced a reduction in depersonalization in an open trial (Sierra et al. 2001), none of nine patients responded to lamotrigine in a placebo-controlled crossover trial (Sierra et al. 2003).

Furthermore, treatment data from a large but uncontrolled and retrospective database have suggested that the combination of a serotonin reuptake inhibitor with lamotrigine may have additive, if not synergic, effects in the treatment of DRD. This report has received considerable attention in the field but requires more rigorous replication.

Naltrexone

An uncontrolled trial of naltrexone, a nonselective opioid antagonist, in 14 patients with DRD found an average 30% reduction in depersonalization/derealization symptoms, with 4 patients showing marked improvement (Simeon and Knutelska 2005). This could be a promising statistic in a disorder with very low placebo response. Although the sample size was too small for meaningful exploration of naltrexone dosing, it is generally recommended to aim for the highest tolerated dose because naltrexone does not have high affinity for the κ-opioid receptors, and there is some evidence that this subsystem may be involved in depersonalization symptoms. Further study of various opioid antagonists in controlled trials is needed.

Benzodiazepines

In our clinical experience benzodiazepines can reduce depersonalization/derealization symptoms in patients with DRD but only in the presence of prominent symptoms of anxiety. In the absence of anxiety there appears to be no benefit, and patients might feel even more "out of it" than at baseline. There are no controlled trials of benzodiazepines with DRD, but their use is widespread. In a retrospective treatment report of 35 pa-

tients with DRD treated with benzodiazepines, 10 reported definite improvement, 8 reported slight improvement, and 17 stayed the same or worsened (Simeon et al. 2003).

Other Pharmacologically Relevant Medication Classes

Stimulants and related medications that enhance cognition (including methylphenidate, bupropion, atomoxetine, modafinil, and donepezil) are empirically used to treat symptoms of DRD; however, there are no clinical trials supporting their use. A retrospective treatment report found that of 9 cases treated with stimulants, no patients reported that their symptoms had definitely improved, 2 patients reported that their symptoms had slightly improved, and 7 patients reported that their symptoms stayed the same or worsened (Simeon et al. 2003). Of 11 cases treated with bupropion, only 1 patient reported improvement (Simeon et al. 2003).

Regarding other antianxiety agents, of 15 cases treated with buspirone, all of the patients reported that their symptoms stayed the same or worsened (Simeon et al. 2003). Successful treatment of depersonalization/derealization symptoms with typical or atypical antipsychotics has not been reported. Of interest in the disorder is the *N*-methyl-D-aspartate (NMDA) system, as ketamine is the quintessential dissociative anesthetic. Trials have not been conducted of NMDA agonists or antagonists and could be of interest. Similarly, given the close association between tetrahydrocannabinol and depersonalization, cannabinoid antagonists could be of interest but have not been studied.

Other Somatic Treatments

An open trial of transcranial magnetic stimulation (TMS) in patients with DRD has shown very promising results (Mantovani et al. 2011). Daily TMS provided for 3 weeks was associated with decreased symptoms in 6 out of 12 patient participants. Five of the six patients received 3 additional weeks of treatment, experiencing a 68% reduction in DRD symptoms from baseline. TMS targeted the right inferior parietal lobule, which is a major sensory integration center in the brain and has been shown to be associated with simulated out-of-body experiences in healthy volunteers. Replication trials would be very worthwhile.

There are no controlled trials of electroconvulsive therapy (ECT) in DRD patients, but in a retrospective report of three patients with DRD treated with ECT, all three reported that they stayed the same or worsened (Simeon et al. 2003). There are also no reports of cranial electric stimulator devices in DRD to date. A recent biofeedback trial yielded disappointing results. Although there are no published data on the use of neurofeedback, some patients have anecdotally reported a definite subjective response to this modality.

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CHAPTER 26

Dissociative Amnesia

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Dissociative amnesia (DA) is an inability to recall important autobiographical information, usually of a traumatic or stressful nature, that is inconsistent with ordinary forgetting. In DSM-5, dissociative fugue (DF) is a subtype of DA (American Psychiatric Association 2013).

DA is a response to overwhelming external circumstances or traumatic events that generate powerful and intolerable affects and/or intense intrapsychic conflicts. Child abuse, wartime trauma, concentration camp experiences, being subjected to torture or atrocities, natural disasters, and civilian violence are highly prevalent in the histories of DA patients (Loewenstein 1991). Childhood interpersonal trauma, especially perpetrated by individuals on whom a child is dependent, may preferentially result in DA and related autobiographical memory deficits (Freyd 1996). DA for life history is significantly related to higher rates and severity, frequency, and violence of physical and sexual abuse. Repeated childhood sexual and/or physical abuse may change memory systems, leading to lack of access for extensive periods of the life history and/or fragmented autobiographical memory (Brown et al. 2007; Edwards et al. 2001). Types of DA are found in Table 26–1.

In treatment, DA is understood as an *adaptive process*, a "safety valve" or "circuit breaker" reflecting the patient's inability to tolerate full conscious awareness of the dissociated material: its narrative, autobiographical contents; overwhelming affects; and the personal meanings of the traumatic events. The underlying assumptions, cognitive models, and representations of interactions for a person's understanding of and conduct in the world are shrouded by amnesia. Historical and dynamic data that may explain central aspects of a patient's character and adaptations are hidden, often leading to self-blame for his or her impairment. If the DA is not addressed therapeutically, the person may remain permanently impaired (Spiegel et al. 2011).

Controversies have arisen about delayed recall for early traumatic experiences (Brown et al. 1998). Expert consensus is that dissociative amnesia or

TABLE 26–1. Types of dissociative amnesia

Type	Description
Localized amnesia	Inability to recall events related to a circumscribed period
Selective amnesia	Ability to remember some, but not all, of the events occurring during a circumscribed period
Generalized amnesia	Failure to recall one's entire life
Continuous amnesia	Failure to recall successive events as they occur
Systematized amnesia	Amnesia for certain categories of memory, such as all memories relating to one's family or to a particular person
Subtype: with dissociative fugue	Purposeful travel or bewildered wandering

Source. Adapted from Spiegel et al. 2011.

delayed recall for prior traumatic experiences occurs and that there are minimal data to support alternative explanations of these phenomena on the basis of fantasy proneness, various types of suggestibility, and/or iatrogenic factors (Brown et al. 1998; Dalenberg et al. 2012; Vermetten et al. 2007). When compared with objective documentation, accuracy of delayed recall of dissociated memory is no different from recall of traumatic events for which there has been continuous memory (Dalenberg 2006).

In acute DA, there is an *acute, florid* dissociative process, usually proximate to acute stressors and/or traumatic events, with major memory impairments for years—if not all—of the person's life history, often accompanied by loss of awareness of personal identity, sometimes presenting after an episode of the DF specifier. In the more common presentation of DA, the amnesia is chronic, covert, and hidden, usually detected only by specific enquiry in the diagnostic interview or during therapy (Loewenstein 1991). These patients report extensive gaps or deletions in recall for aspects of their past autobiographical history and, at times, for aspects of their recent history. They may have difficulty in recall of traumatic events or for periods of their life when multiple traumatic events occurred and may also have autobiographical memory fragmentation.

Commonly, the latter patients have comorbid posttraumatic stress disorder (PTSD) or partial PTSD, in which the intrusive symptoms may develop or worsen as DA remits. They commonly have comorbid mood, obsessive-compulsive, substance use, eating, impulse control, and/or personality disorders that may need to be addressed psychopharmacologically and/or with specialized interventions (Loewenstein 2001).

Although most data about DA treatment come from case reports or small case series, there is clinical consensus for the phasic treatment of this disorder (Spiegel et al. 2011): 1) a phase of achieving safety and stability; 2) a phase of reviewing and processing traumatic memories and grieving their impacts, implications, and attendant losses; and 3) a phase that develops the foundation for an integrated self and a life relatively free from posttraumatic symptoms and concerns (Her-

man 1992). These phases may overlap because trauma memory material may need to be addressed, if only in a more cognitive and limited way, before the goals of the phase of safety are attained; because work with patients who have suffered recurrent traumatization rarely allows all traumatic material to be addressed simultaneously; and because better overall living and adaptation are the basic goal of all trauma treatment and the focus of all stages (Loewenstein and Welzant 2010).

The patient's relationship with the therapist is crucial. Facilitating the patient's putting his or her trauma story into words, often for the first time, with a responsible, supportive, nonjudgmental, and caring witness is essential in restructuring the meaning of the experience and transforming disruptive, overwhelming traumatic memories into normal, albeit unpleasant, memories. Authorities concur that the therapist should be warm, at least moderately expressive, and friendly. Failing this, the traumatized person usually experiences bland responses as indifference, if not rejection and shaming (Kluft and Loewenstein 2007). On the other hand, traumatic transference is ubiquitous in trauma treatment: the patient unconsciously identifies the therapist with whoever or whatever inflicted the trauma (Spiegel 1989).

Safety is the most important aspect of trauma treatment. Both acute and chronic DA may be psychological alternatives to suicide or to interpersonal violence (Gudjonsson and Haward 1982). Suicide attempts, and even completed suicide, may occur if amnestic barriers are removed precipitously with inadequate stabilization (Takahashi 1988). Other safety issues include substance abuse; dangerousness to others, including the minor children of the patient; high-risk behaviors (e.g., reckless driving, wandering in unsafe places); eating disorders; lack of food, clothing, and shelter; and lack of attention to medical needs.

In acute DA, the person's physical safety is the first concern: removal from the traumatizing environment; evaluation and treatment of medical problems; and provision of shelter, food, and sleep. Providing psychological first aid may allow the beginning of resolution of an acute traumatic DA episode (Brymer et al. 2006). As many as three-quarters of acute DA patients recover memory for identity and life history after they are restored to safety and/or come to clinical attention, as spontaneous remission, in the course of the psychiatric history, or with specific suggestions for and reassurances about memory recovery (Abeles and Schilder 1935; Loewenstein 2001; Tureen and Stein 1949). Amnesia and fugue may be a response to rape or sexual assault (Kaszniak et al. 1988), so individuals with DA or DF may require evaluation for genital or rectal injury, pregnancy, and/or sexually transmitted diseases.

Safety issues for patients with chronic DA are managed as part of longer-term psychotherapy for resolution of the psychological sequelae of the events producing the amnesia. Many of these patients will fit the construct of complex posttraumatic stress disorder, with dimensional problems and deficits including affect regulation deficits; liability to dissociation; problems with sense of self and body image; problems forming relationships and stable attachments; deformations in self-attribution and systems of meaning: the world seen as dangerous and traumatizing and the self as damaged, shameful, defective, and responsible for traumatization; and self-destructiveness, including suicide attempts, substance abuse, self-injury, and risk-taking behaviors (Courtois and Ford 2009).

Psychoeducation is important in the initial phase of treating DA. The patient is helped to develop an organizing framework to understand his or her condition and symptoms and the treatment process. The amnestic patient is educated about the adaptive nature of amnesia and the need to be respectful, careful, and deliberate in attempting to overcome it.

Self-harmful behaviors or substance abuse are usually self-regulating, state-altering behaviors to attempt control of intense dysphoria, intrusive flashback symptoms, or acute dissociative episodes. They may represent the patient's attempts to *keep* traumatic material in a state of amnesia. The clinician reframes these behaviors as attempts at adaptation, not simply as "bad" behaviors, and explains that creation of safety is essential to successful treatment. The patient is helped to master more adaptive coping, self-regulation, and symptom-management skills. Approaching self-destructive symptoms in this way is more successful than approaches that are based on behavioral control.

The literature on dissociative amnesia underscores the importance of *permissive* suggestions for recall. The patient with dissociative amnesia has profound concerns about control and trust. Enabling the patient to experience a sense of control over the pace of recollection for dissociated information is essential. Attempts to work with DA may produce flashbacks, sometimes so severe that the patient loses awareness of contemporary reality, experiencing himself or herself as literally in a past traumatic event. Symptom management skills are helpful, including relaxation and deep breathing, containment and grounding skills, imagery, and hypnotic skills. *Hypnotic interventions should be undertaken only by clinicians certified in clinical hypnosis who have had additional, specific training in hypnotic approaches to trauma and dissociation.*

Grounding includes asking the patient to breathe deeply and slowly, open his or her eyes, and/or redirect the gaze (if the patient appears to be visualizing and interacting with a past experience); look around, recognize, and reorient to the office, treatment room, or outside; feel his or her feet on the floor and/or hands on the chair; and use all five senses to connect with current reality. The therapist can concretely orient the patient by stating his or her name, the location, and the date as well as reminding the patient that the event is in the past and that he or she has survived it and is in the present. After such an event, the clinician may give suggestions for DA: the material may be too overwhelming to be worked on without additional stabilization and preparation and must be psychologically sequestered.

The interventions for memory recovery differ somewhat in the treatment of the two types of DA. In acute DA, the goal is to rapidly restore memory for identity and life history. Specific memory enhancement techniques such as hypnosis may be introduced quickly. Informed consent includes education for all DA patients about the nonphotographic, reconstructive nature of memory. In addition, when hypnosis or pharmacologically facilitated interviews are used in DA patients, education is provided that recalled memories should be regarded as no more or less reliable than recall of any other memory (American Society of Clinical Hypnosis Committee on Hypnosis and Memory 1994; Cardena et al. 2000).

Free-recall procedures can lead to recollection of dissociated memories. The patient reflects on his or her inner experience and reports whatever occurs. The

patient is asked to associate with whatever comes to mind, even if seemingly irrelevant or inconsequential, and to continue the chain of associations. Context reinstatement and state-dependent recall can be added to the free-association techniques by focusing the patient on the time period(s) for which there is DA and/or the affects and somatic sensations related to DA.

In the case of generalized DA with complete loss of memory for identity and/or life history, context reinstatement and state-dependent recall should be directed at whatever thoughts, images, memories, or emotions the patient has. Use of automatic writing, typing on a number pad, or similar techniques can provide memory material (Loewenstein 1991). In acute DA, if free-recall procedures are unsuccessful, hypnotic and related techniques can be introduced, including age regression and/or affect bridge techniques, although pacing must be used very carefully to titrate the intensity of the recall (Hammond 1990; Watkins 1992).

In DA treatment, clinicians should use nonleading, nondirective questioning to the extent possible, for example, "and what happened after that…and then…and what happened next…and how did you feel then…and what did you think about that?" etc. Inquiry about affects that have not been prominently displayed or discussed may help to resolve amnesia, including tracking which affects (e.g., despair, sorrow, grief, horror, shame, helplessness, rage, guilt, confusion, anguish) are most and least available to the patient. The clinician can help the patient name specific experiences and emotions, such as terror, shame, horror, confusion, helplessness, grief, and rage.

The clinician may also give reality-orienting information, such as "you are safe now, you are in the present," as well as normalizing information, such as "it is natural for someone to be very frightened when his ship is on fire and sinking…" that the traumatized person may not realize is a normal response to danger. Resolution of DA usually requires the patient's repeatedly processing dissociated material in a number of different sessions, at different levels of affective intensity (van der Hart et al. 1993).

Often some aspect of the traumatic event is central to resolving the amnesia yet is withheld despite the processing of other aspects. For example, a patient who has worked on memories of father-daughter incestuous assaults without the material losing its disruptive force ultimately learns that her mother had walked in on an assault only to turn and walk away. Likewise, many rape traumas remain unresolved until the victim shares her mortification and horror over experiencing sexual arousal during the assault. Only when "unspeakable details" are shared and processed do the intrusive symptoms begin to diminish.

Some patients' DA or DF conditions are generated by intrapsychic conflict, notwithstanding earlier traumatic experiences. Their wishes or behaviors are in conflict with deeply held moral values and behavioral standards. Indiscretions or powerful urges to commit indiscretions—personal, sexual, financial, etc.—may trigger dissociative episodes. In other cases, conflict concerns behavior that is not morally problematic itself (e.g., entering the military to follow in the footsteps of an abusive parent) but conflicts with other strongly held convictions or values (e.g., building a family life by remaining at home).

Patients are helped to tolerate these affects or conflicts without resort to dissociative defenses. They may have diffi-

culty tolerating anger or violent impulses, often triggering recall of earlier experiences with physical violence or other traumas. Therapeutic efforts are directed toward reducing patients' brutally unreasonable, and often conflicting, expectations for themselves, as well as the guilt and shame that accompany and/or play an etiological role in dissociation. Therapy not only addresses the acute dissociation, it endeavors to explicate, work through, and restructure the patient's thoughts, feelings, self-perceptions, and character issues related to the antecedent traumata.

In chronic DA, amnesia is addressed in the context of long-term psychotherapy. Often DA begins to spontaneously remit in the course of a well-structured phasic trauma treatment. Interpretation of transference issues, particularly traumatic transference themes, and resolution of trauma-based cognitive distortions may help in recall of dissociated memory (Lindy 1989; Loewenstein 2001). Direct attempts to overcome DA in these patients should be undertaken only very gradually because there usually are multiple trauma memories, and too rapid uncovering may lead to overwhelming PTSD intrusions with dyscontrol and self-destructive crises. Here, hypnotic techniques are used primarily for distancing and attenuation of the intensity of memory material.

Other than pharmacologically facilitated interviews, there is no specific psychopharmacological approach to DA. Psychopharmacological treatment is pragmatically directed to comorbidities: mood, anxiety, psychotic, impulse-control, obsessive-compulsive, attentional, and other disorders. A variety of agents have been used for pharmacologically facilitated interviews, including sodium amobarbital, thiopental (Pentothal), oral benzodiazepines, and amphetamines (Ruedrich et al. 1985). No studies confirm the relative efficacy of any of these agents. Pharmacologically facilitated interviews are usually more helpful for acute DA (Poole et al. 2010). The current standard of care views these methods as "conscious sedation" that must be performed with an anesthesiologist where resuscitation equipment is available. Video and/or audio recording of the procedure is mandatory because patients may have amnesia for the interview. Informed consent for these procedures should include discussions of memory, recording the interview, and medical complications.

During the final phases of DA treatment, effective hypnotic interventions may include those for integration, mastery healing, wholeness, calm, mature reflection, peace, quietude, and serenity; letting go of the past; turning to the present and future; and reuniting traumatically dissociated aspects of self.

As DA treatment draws to a conclusion, the patient experiences the dissociated information as continuous autobiographical memory, able to be recollected or put aside. There should be no intrusive images, affects, sensations, or residual memory gaps. Issues once fraught with conflict, guilt, or shame are tolerated in consciousness. Responsibility for shortcomings, failings, and lapses should be accepted without paralyzing shame or guilt. What previously seemed overwhelming and disruptive should be experienced with a sense of perspective. Energy is available for life tasks and avocations and for looking toward a nontraumatic future. In the long-term treatment of DA, as in other complex posttraumatic disorders, formal termination of psychotherapy may not occur. The patient may continue in supportive treatment and/or long-term medication management. The patient may need to engage in more active treatment to man-

age life stresses, developmental issues, and severe medical problems, among many other issues.

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CHAPTER 27

Posttraumatic Stress Disorder

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There has been a proliferation of posttraumatic stress disorder (PTSD) research over the past few decades. Even when restricting search results to treatment outcome articles in English on adults ages 18–65, a PubMed and PsycINFO search returned more than 370 unique articles published since 1988. Stricter search criteria of at least one comparison group; group numbers of at least 10 in data analyses; and the use of valid, reliable measures yielded 126 unique PTSD treatment studies. These findings exclude ongoing trials that have yet to analyze or publish results. A ClinicalTrials.gov search returned 355 ongoing studies of PTSD treatment: 235 active, recruiting; 74 active, no longer recruiting; and 46 active, not yet recruiting. Although such rapid growth in this field of research is both encouraging and fascinating for mental health and clinical science, it leads to a potentially overwhelming, constantly evolving literature base that makes it difficult for clinicians and clinical scientists to remain current.

Accordingly, we seek to provide a synthesis of reviews, especially in summarizing the two most common treatment approaches of trauma-focused cognitive-behavioral therapy (CBT) and antidepressant-focused pharmacotherapy. Furthermore, keeping in mind the ever-expanding PTSD treatment literature, this chapter includes newer treatment methods, some of which combine currently used techniques, while others represent more novel approaches.

Regardless of the DSM-5 changes in PTSD's classification and diagnostic criteria (American Psychiatric Association 2013) (see Table 27–1 for a comparison of

the former and current DSM criteria for PTSD), research on the course of PTSD symptoms demonstrates that their occurrence is almost ubiquitous immediately after trauma; however, the symptoms of reexperiencing, avoidance, and hyperarousal will eventually diminish with time for most individuals (Rothbaum et al. 1992). Although most trauma survivors will experience an improvement in PTSD symptoms, trauma is unfortunately a universal experience, as studies estimate that 89.6% of Americans have been exposed to a traumatic event in their lifetime (Breslau 2009). Such common exposure results in fairly high prevalence rates of PTSD, which afflicts approximately 6.8% of Americans (Kessler et al. 2005) and likely a greater proportion of individuals living in less developed, non-Western nations dealing with wars, forced migration, and higher rates of violence (Mletzko and Dunlop 2011).

Fortunately, despite the pervasiveness of trauma, there is an array of PTSD treatments available, with several types supported by strong clinical research. In this chapter, we present a comprehensive assessment of the evidence for the various treatment approaches to PTSD, beginning with psychotherapy and pharmacotherapy, the approaches that have been studied most extensively. We then discuss emerging, promising treatments, including medication-enhanced psychotherapy (MEP), early interventions, alternative delivery methods, and complementary and alternative medicine (CAM). Finally, we compare our evaluation of the literature with recent treatment guidelines (Forbes et al. 2010; Institute of Medicine 2012) to provide recommendations for the best currently available treatments, the most promising areas of treatment research, and the treatment approaches in need of further research.

Psychotherapy

Because nearly 40% of individuals diagnosed with PTSD maintain significant symptoms a decade after onset (Kessler et al. 1995), it is fortunate that there are strong psychotherapeutic treatments available. Reviews of the treatment guidelines for PTSD demonstrate the most evidence for trauma-focused psychotherapy (Forbes et al. 2010; Institute of Medicine 2012). A meta-analytic review of 26 studies of psychotherapy for PTSD revealed strong responses to cognitive-behavioral approaches (Bradley et al. 2005). Specifically, across all treatments in all 26 studies, of patients who entered treatment (intent to treat), 56% no longer met criteria for PTSD and 44% met criteria for clinically meaningful improvement (Bradley et al. 2005). As expected, response to treatment was higher in patients who completed treatment, with rates of 67% for diagnostic change and 54% for clinically meaningful improvement (Bradley et al. 2005).

There are several psychological treatment options, ranging from interpersonal, dynamic, eclectic, and cognitive to cognitive-behavioral; however, CBT has garnered the most empirical evidence and is recommended, as a Level A treatment, in all of the major treatment guidelines. Indeed, a recent summary of major meta-analyses of psychotherapy for PTSD (N=48 studies) concluded that trauma-focused CBT is an effective treatment with large effect sizes (Bryant 2011). CBT techniques focus on having the patient confront rather than avoid his or her traumatic memories while also confronting distorted cognitions surrounding the trauma that allow PTSD symptoms to persist. Although slightly different techniques, prolonged exposure (PE), cogni-

TABLE 27–1. Comparison of DSM-IV-TR and DSM-5 diagnostic criteria for posttraumatic stress disorder

DSM-IV-TR	DSM-5
Criterion A: Stressor 1. Person experienced, witnessed, or been confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others. 2. Person's response involved intense fear, helplessness, or horror.	**Criterion A: Traumatic event** Exposure to actual or threatened death, serious injury, or sexual violation in one (or more) of the following ways: 1. Directly experiencing the traumatic event(s). 2. Witnessing, in person, the event(s) as it occurred to others. 3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental. 4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related).
Criterion B: Intrusive recollection Person persistently reexperiences the traumatic event in at least one way (e.g., recurrent and intrusive distressing recollections or dreams, acting or feeling as if traumatic event were recurring).	**Criterion B: Intrusion** Presence of one (or more) intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred (e.g., recurrent, involuntary, and intrusive distressing memories or dreams, dissociative reactions).
Criterion C: Avoidance or numbing At least three symptoms of persistent avoidance of stimuli associated with trauma and numbing of general responsiveness are present (and were n	**Criterion C: Avoidance** Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evi- distressing mem- th.

TABLE 27–1. Comparison of DSM-IV-TR and DSM-5 diagnostic criteria for posttraumatic stress disorder *(continued)*

DSM-IV-TR	DSM-5
Criterion D: Hyperarousal At least two persistent symptoms of increased arousal are present (and were not present before the trauma).	**Criterion D: Negative alterations in cognitions and moods** Two (or more) negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred.
Criterion E: Duration Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month (acute if duration less than 3 months, chronic if 3 months or more).	**Criterion E: Arousal and reactivity** Two (or more) marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred.
Criterion F: Functional significance The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.	**Criterion F: Duration** Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month
	Criterion G: Functional significance The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
	Criterion H The disturbance is not attributable to the physiological effects or a substance or another medical condition

Note. In addition to the differences displayed above, for DSM-5, PTSD was moved from anxiety disorders into a new diagnostic category, trauma- and stressor-related disorders.

Source. DSM-IV-TR criteria adapted from National Center for PTSD Web site: National Center for PTSD 2007. DSM criteria for PTSD. Retrieved from: http://www.ptsd.va.gov/professional/pages/dsm-iv-tr-ptsd.asp. DSM-IV-TR criteria adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000; DSM-5 criteria adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition. Arlington, VA, American Psychiatric Association, 2013. Copyright 2

tive processing therapy (CPT), and eye movement desensitization and reprocessing (EMDR) are all forms of CBT with scientifically validated efficacy that are highly recommended in treatment guidelines. We also discuss other less utilized and validated CBT- and non-CBT-based approaches.

Cognitive-Behavioral Therapy

Exposure Therapy

Exposure therapy (ET), which is based on animal models of fear conditioning and extinction, seeks to reduce the fear associated with a trauma memory by repeatedly exposing the patient to that memory and reminders. Theoretically, this repeated exposure habituates the patient to the fear reminders, thereby reducing anxiety and thus avoidance of the memory and reminders (Rothbaum and Davis 2003). In turn, by no longer avoiding the memory, patients can emotionally process what happened to them and thus correct distorted cognitions regarding the trauma, with the ultimate goal of learning that their fear is unwarranted and often also relieving other painful emotions such as shame and guilt. Presentation of trauma-related stimuli can occur through imaginal, in vivo, or virtual reality exposures while also combining cognitive therapy (CT) techniques, specifically, Socratic questioning, during emotional processing. PE is a specific program of ET that includes imaginal and in vivo exposure, processing, education about common responses to trauma, and breathing relaxation to make the exposure helpful and therapeutic (Foa et al. 2007).

Among the various other treatment modalities, ET is considered the gold standard and one of the first-line treatments for PTSD. Indeed, the Institute of Medicine (IOM) report on 37 pharmacotherapy and 53 psychotherapy randomized clinical trials (RCTs) for PTSD concluded that only exposure therapy demonstrated sufficient evidence for efficacy (Institute of Medicine 2008). Furthermore, a review of CBT for chronic PTSD (symptom duration of at least 3 months) for the International Society for Traumatic Stress Studies (ISTSS) practice guidelines indicated that PE, with 24 randomized and 9 nonrandomized trials demonstrating treatment efficacy, had the most evidence (Cahill et al. 2009).

Using stricter eligibility criteria, a meta-analytic review comparing ET with control conditions found large effect sizes in favor of ET in PTSD treatment response (Powers et al. 2010). However, there were no significant differences in improvement of PTSD symptoms between ET and other treatments: CPT, CT, EMDR, and stress inoculation training (SIT). Still, the meta-analysis of 658 patients from 13 studies showed that patients who received ET maintained their treatment gains at follow-up assessments and improved better than 86% of control group patients, who were typically assigned to either supportive counseling or wait list (Powers et al. 2010). This finding that PE significantly improved PTSD symptoms but did not differ in efficacy from CPT, CT, EMDR, or SIT is consistent with several other meta-analyses that primarily compared CBT-based and other psychotherapy treatments (Benish et al. 2008; Bisson and Andrew 2007; Bradley et al. 2005).

By including only studies that directly compared active treatments intended to be therapeutic, Benish et al.'s (2008) meta-analysis improved on prior reviews that lumped active treatments such as psychodynamic therapy into a heterogeneous group with such conditions as

supportive counseling. With 15 studies making 17 comparisons for a total of 958 patients, this meta-analysis was the largest direct comparison conducted. Ideally, more direct comparison trials in the PTSD treatment literature are needed to test for heterogeneity among active treatments (Benish et al. 2008). Even a very recent review (Nayak et al. 2012) of seven clinical research "gold standard" (Foa and Meadows 1997) studies comparing ET with other active treatments as well as controls found ET superior to controls but not different from other active treatments, with the exception of present-centered therapy. The use of some exposure components in CPT, EMDR, and SIT could explain the similar findings to ET, but more research needs to be conducted comparing these active treatments and dismantling the components of each treatment to better elucidate this result.

Undoubtedly, there is a need for greater scientific understanding of the active components of effective psychotherapy such as PE. Nevertheless, ET remains recommended by all of the major treatment guidelines as essentially a first-line psychotherapy or first-level rating intervention for PTSD (Forbes et al. 2010; Institute of Medicine 2012). Moreover, ET's demonstrated efficacy appears to generalize beyond the typically studied female assault survivors to other trauma types and populations (e.g., persons in motor vehicle accidents, civilians, combat veterans, men, war refugees or survivors) as well as to other cultures (Nayak et al. 2012).

Cognitive Processing Therapy

CPT focuses on changing maladaptive cognitions or thoughts surrounding the trauma instead of reducing fear via exposure. Developed by Resick and Schnicke (1993), CPT's three main phases involve 1) psychoeducation and identification of "stuck points" (Chard et al. 2012); identification of overgeneralized, unhelpful beliefs regarding the trauma; 2) a narrative, written exposure component designed to have patients start to challenge these beliefs; and 3) further challenging and reshaping of stuck points into healthier thought patterns. Overall, the goal of this treatment is to change the way the patient thinks about what happened to him or her.

Good evidence exists supporting the efficacy of CPT for PTSD treatment. Both the IOM (Institute of Medicine 2008) and various other major guidelines (Forbes et al. 2010) recommend CPT as a first-level psychological intervention for PTSD. Although CPT lacks any exclusive meta-analytic studies of its efficacy, several previously described reviews report that CPT significantly decreased PTSD symptoms and was comparable in efficacy to other active treatments, including PE (Benish et al. 2008; Bisson and Andrew 2007; Bradley et al. 2005; Nayak et al. 2012; Powers et al. 2010). Most treatment outcome studies of CPT have been conducted with interpersonal trauma populations and females, demonstrating significant symptom improvement in both group and individual treatment settings (Chard et al. 2012). However, there is emerging evidence that CPT is also effective for treating chronic PTSD in combat veterans (Monson et al. 2006) and for improving PTSD symptoms in traumatized refugees in developing countries (Schulz et al. 2006). More studies that can replicate these positive results are still needed.

Why treatments like CPT and PE seem equally efficacious remains unclear. Seeking to parse out the active ingredients of CPT, Resick and colleagues (2008) conducted an RCT of 150 female assault

survivors comparing the full protocol of CPT; the narrative, writing exposure component alone; and the cognitive therapy phase alone. Unexpectedly, findings indicated that each treatment group exhibited significantly improved PTSD symptoms with no differences between full CPT and the two separate treatment components (Resick et al. 2008). Also interesting was the finding that cognitive therapy alone was superior to exposure-based writing alone in reducing symptoms (Resick et al. 2008). Despite these encouraging findings that could eventually provide more PTSD treatment options, more dismantling RCTs are needed to replicate these initial results before individual CPT components can be recommended as effective PTSD treatments.

Eye Movement Desensitization and Reprocessing

Slightly more controversial but still highly supported as efficacious, EMDR is an eight-phase treatment that involves such cognitive-behavioral elements as trauma-focused exposure and cognitive therapy but with the added component of saccadic eye movements or some sort of bilateral stimulation. The key difference to note in EMDR is its broad approach. There is some debate regarding the mechanism of action of EMDR in treating PTSD and whether the eye movements are necessary. Accordingly, there have been many speculative critiques of EMDR (Spates and Rubin 2012) and even research suggesting that EMDR may still exhibit treatment effects without the inclusion of eye movements as per the protocol (Spates et al. 2009).

Regardless, the treatment literature shows EMDR to be efficacious for PTSD. Most of the treatment guidelines recommend EMDR as a first-level psychotherapeutic approach with good evidence for PTSD treatment, with the exceptions of the American Psychiatric Association (APA) and the Australian National Health and Medical Research Council, which noted respectively that it had moderate evidential support and the strongest level of evidential support when in vivo exposure was included (Institute of Medicine 2012). Another exception in the treatment guidelines for EMDR is the IOM, which noted that inadequate evidence was available to recommend it for treating PTSD (Institute of Medicine 2008). Indeed, EMDR lacks the number of studies supporting its efficacy in contrast to ET, but a recent review of seven EMDR treatment studies from 2000 to 2010 revealed that EMDR was superior to control conditions in each study and was occasionally superior, although sometimes inferior, to exposure as well (Spates and Rubin 2012).

To our knowledge, only one meta-analysis (N=38 studies; Bisson et al. 2007) has shown EMDR to be weaker than trauma-focused CBT, although EMDR still significantly improved PTSD symptoms. Spates and Rubin (2012) also reviewed seven extant meta-analyses that included EMDR (two exclusively focusing on EMDR), noting that all these studies found it to be efficacious for treating PTSD and generally equal in efficacy to CBT. Still lacking is evidence that the use of eye movements is an essential component of EMDR. Taken all together, these varied results suggest that although EMDR appears to be a good treatment for PTSD, whether its efficacy is relatively equal to ET and trauma-focused CBT appears to be equivocal. Researchers and clinicians need to continue methodically rigorous investigations comparing these treatments and uncovering the therapeutic components of EMDR.

Combined and Other Forms of Cognitive-Behavioral Therapy

There are several other theoretically based forms of CBT. Although less studied, they have demonstrated efficacy as PTSD treatments. Approaches focused on reducing anxiety when the patient is reminded of the trauma or anxiety management techniques have some evidential support, with the most for SIT. An initial mix of uncontrolled investigations, RCTs, and case studies in rape survivors indicated positive treatment effects of SIT on a variety of PTSD-, fear-, and anxiety-related measures (Ressler and Rothbaum 2009). Bradley and colleagues' (2005) previously mentioned meta-analysis of psychotherapy for PTSD found that the variations of SIT examined in three studies in the review were efficacious, with the majority of patients achieving clinically meaningful improvement. Finally, though SIT does not always receive the highest rating level for recommendations from treatment guidelines, several such guidelines recommend it for PTSD, although it has not been examined for use in military populations (Forbes et al. 2010).

Less studied behavioral approaches such as relaxation and systematic desensitization (SD) are not recommended as stand-alone PTSD treatments (Ressler and Rothbaum 2009). Relaxation techniques such as breathing are used in the PE protocol, but more RCTs or dismantling studies are needed before relaxation alone can be a recommended treatment. SD is no longer recommended for the treatment of any anxiety disorder. Ressler and Rothbaum's (2009) review of psychosocial PTSD treatments further noted that inconsistent findings in comparing relaxation, SD, and flooding led to elimination of SD alone as a recommended treatment for PTSD. Still, remnants of SD, such as in vivo exposure, remain a key element of the strongly recommended, often-used PE.

Last, several combined CBT-based approaches have been investigated. These combinations, such as SIT with PE, social and emotional rehabilitation, and exposure with cognitive restructuring (a cognitive-based therapy), have proven efficacious for treating and significantly improving PTSD symptoms but have been studied far less extensively than PE, CPT, and EMDR (Ressler and Rothbaum 2009). Studies that compared combinations of exposure with CBT showed that these approaches led to clinically significant improvements in the majority of patients with PTSD who completed treatment; they were also as efficacious in treating PTSD as PE or CBT alone (Bradley et al. 2005). Results from these lesser studied CBT-based treatments are promising because they provide alternatives to PE, CPT, and EMDR. Indeed, combined, trauma-focused CBT approaches and SIT are recommended in several guidelines, but some of these other forms of CBT, such as relaxation and SD, lack sufficient and rigorous evidence to be recommended as treatments (Forbes et al. 2010; Institute of Medicine 2012).

Other Psychotherapy

Although treatment of traumatized individuals with psychodynamic psychotherapy and hypnosis dates back to Freud, there is a dearth of good scientific evidence for such approaches. Specifically, both the IOM (Institute of Medicine 2008) and Cochrane Database of Systematic Reviews (Bisson and Andrew 2007) concluded that hypnosis and psychodynamic therapy lacked sufficient empirical support and that research on these approaches lacked rigorous methodology such as randomization and appro-

priate control groups. There is, however, one RCT demonstrating superiority of both hypnosis and psychodynamic psychotherapy to a wait-list control condition (Brom et al. 1989). Thus, the IOM (Institute of Medicine 2008), the most rigorous of meta-analytic reviews and guidelines, noted that insufficient evidence existed to make a conclusion regarding the efficacy of hypnosis or psychodynamic therapy. Still, as seen in Forbes and colleagues' (2010) synthesis of the available PTSD treatment guidelines, psychodynamic therapy has some second-level ratings (from the U.S. Department of Veterans Affairs/Department of Defense [VA/DoD] and ISTSS guidelines), indicating that it may be useful but lacks strong evidence from clinical trials. Additionally, a recent IOM summary of treatment guidelines (Institute of Medicine 2012) concluded that there was weak to moderate evidence for psychodynamic psychotherapy, but hypnosis could not be given a recommendation for or against its use. Undoubtedly, hypnosis and psychodynamic therapy require better methodologically designed studies before they can be recommended for PTSD treatment (see Ressler and Rothbaum 2009 for a more in-depth review).

There remain promising psychotherapeutic treatments with an emotional focus, namely, acceptance and commitment therapy (ACT), dialectical behavior therapy (DBT), and skills training in affective and interpersonal regulation (STAIR). Though somewhat theoretically based in CBT, ACT instead emphasizes changing an individual's attitude or emotions surrounding trauma-related negative thoughts. The goal is to accept symptomatic abnormalities or negative thoughts as part of someone's unique emotional experience. Currently, research has shown support for ACT in treating PTSD in only some case studies, with much more extensive research needed (Kearns and Rothbaum 2012). Although DBT is strongly supported as an evidence-based practice for patients with borderline personality disorder, who often have histories of trauma exposure, it has yet to be rigorously tested for PTSD treatment (Kearns and Rothbaum 2012). Developed by Linehan (1993), DBT involves cognitive-behavioral techniques along with mindfulness, acceptance, and even some exposure with the goal of improving emotion regulation and reducing the tendency for suicidal behavior often observed in borderline patients. Finally, STAIR is often utilized as a preparation for other CBT approaches rather than as a free-standing treatment. Despite its emphasis on the important link between emotional problems and poor response to treatment, STAIR is fairly similar to CBT, as it also makes significant use of PE (Kearns and Rothbaum 2012). Positive results were found for STAIR in a clinical trial to treat PTSD, but whether treatment effects can be attributed to the emotion regulation component or the exposure component remains unclear (Kearns and Rothbaum 2012). Therefore, STAIR requires more research to parse out the active ingredients of the treatment and to clarify the link, if any, between emotion regulation and efficacy of PE. Overall, these more recently developed treatments show promise but require much more investigation, especially via RCTs, before we can draw proper conclusions as to their efficacy for PTSD treatment (see Kearns and Rothbaum 2012 for a more in-depth review).

Pharmacotherapy

Unfortunately, despite the strong evidence and recommendations for ET and trauma-focused CBT, not all patients with

PTSD will respond to psychotherapy, will have it available, or will be willing to try it. Thus, medication continues to be a viable treatment option; however, its efficacy may not be as great as that of CBT. Most practice guidelines recommend antidepressants, usually selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine as first-line PTSD treatments; the lone exception is the United Kingdom's National Institute for Health and Clinical Excellence (NICE; Forbes et al. 2010; Institute of Medicine 2012). The Cochrane Database review of pharmacotherapy for PTSD, one of the more rigorous meta-analyses, observed medication superiority relative to placebo with response rates of 59.1% in patients receiving medication compared with 38.5% in patients receiving placebo (Stein et al. 2006). Still, the most rigorous review of therapies for PTSD found insufficient evidence to reach a conclusion on the efficacy of any medication for PTSD (Institute of Medicine 2008). It must be remembered that the IOM report is not a clinical practice guideline but rather a critique of the scientific rigor of clinical trials on PTSD. In that regard, one might challenge the IOM's conclusion, or lack of a conclusion, regarding pharmacotherapy as much too strict. Indeed, one expert dissenting member on the committee asserted that the IOM's conclusion was unwarranted because many negative results for SSRI trials involving combat veterans (with very chronic and refractory PTSD) may have nullified generally positive findings observed in civilian populations (Stein et al. 2009). Essentially, different guidelines and meta-analytic reviews have yielded varying results about pharmacotherapy for PTSD, with the majority of these guidelines recommending SSRIs and SNRIs as first-line treatments or medications for PTSD.

In this section, we first focus on antidepressants, typically the most studied medication for PTSD, with an emphasis on SSRIs. We then discuss other psychotropic pharmacological treatments, with particular attention to the use of atypical antipsychotics (AAs) as augmentation strategies. We will also examine evidence from clinical trials with nonpsychotropic medications (e.g., antiadrenergic and anticonvulsant medications). Last, new pharmacological techniques aimed at early intervention for and prevention of PTSD or at augmenting psychotherapy are discussed separately in later sections of this chapter.

Antidepressants

SSRIs

The SSRIs sertraline and paroxetine are the only medications with a U.S. Food and Drug Administration (FDA) indication for PTSD. Although the IOM and NICE guidelines did not recommend any pharmacotherapy as a first-line PTSD intervention, there is ample evidence from meta-analytic reviews and other guidelines to suggest that SSRIs are valid PTSD treatment options. The Cochrane Database review provides the strongest evidence for SSRIs. In this meta-analysis of 35 RCTs (4,597 patients) of various psychiatric medications, nearly half of the trials, 17, found that medication significantly reduced PTSD symptoms compared with placebo, with the 12 included SSRI studies contributing 82.4%, the most of all medications, to the overall effect size (Stein et al. 2006). Among the various SSRIs analyzed, both paroxetine and sertraline demonstrated efficacy, whereas citalopram and fluoxetine did not, a finding consistent with the aforementioned FDA indications (Stein et al. 2006). Being the most comprehensive pharmacotherapy meta-analysis (Stein et al. 2009),

the Cochrane Database review's results suggest that SSRIs ought to be considered first-line pharmacological interventions for PTSD. Most treatment guidelines are consistent with the Cochrane Database review's findings, as four of six major guidelines recommend SSRIs as a first-line pharmacotherapy for PTSD (Forbes et al. 2010). Furthermore, in a review of treatment guideline quality, Stein and colleagues (2009) noted that six of nine meta-analytic reviews and guidelines recommended some SSRIs as first-line PTSD treatments, and another two recommended them as second-line treatments. Finally, Stein and Ipser's (2011) summary of several large pharmaceutical trials for SSRIs conveys a large evidence base for their efficacy, as six of seven studies (2,046 patients) found the SSRIs paroxetine, sertraline, and fluoxetine superior to placebo.

The IOM (Institute of Medicine 2008) incorporated more stringent criteria and thus excluded many studies included in other guidelines and meta-analyses of pharmacotherapy. The only other guideline to not recommend SSRIs as first-line PTSD medications, the NICE review, used the somewhat arbitrary criterion of an effect size more than 0.5 for clinical significance (Stein et al. 2009). This fairly subjective interpretation for clinical significance ignores improvement in other outcomes such as clinical global impressions, which can denote improvement in patients who may still have fairly high PTSD symptoms but have clinical improvement. This issue with the NICE guideline is indicative of a larger problem of inconsistent definitions of clinical significance and treatment response in PTSD research. In addition, the NICE guideline included unpublished, nonpeer-reviewed studies in its analysis, thereby raising serious questions about the scientific quality of all the studies that were considered. Thus, the IOM and NICE reviews, despite their high quality of design (Stein et al. 2009), have their limitations. Other than the IOM (Institute of Medicine 2008) and NICE, there is fairly consistent agreement among the various guidelines for the use of SSRIs as first-line pharmacotherapy interventions for PTSD.

Other Antidepressants

Originally, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were the primary antidepressants used to treat PTSD. With the development of SSRIs and SNRIs, which have less intense side effects, TCAs and MAOIs represent less commonly used, albeit efficacious, medications for PTSD. Positive results have been observed with the TCAs imipramine and amitriptyline and the MAOI phenelzine (Friedman et al. 2009; Rothbaum et al. 2011), but mixed or negative results for TCAs and MAOIs were reported in the Cochrane review (Stein et al. 2006). The strongest support for these two older antidepressant classes can be seen in Stein and colleagues' (2009) review of meta-analyses and guidelines for PTSD treatment. Their synthesis of guidelines suggests TCAs and MAOIs have a fairly large amount of evidence for efficacy, as seven of nine treatment guidelines recommend at least one agent from both of these medication classes. Only one of the nine guidelines recommends just TCAs, while the IOM guidelines (Institute of Medicine 2008) recommends no forms of pharmacotherapy (Stein et al. 2009). Additionally, another recent review of guidelines demonstrated that of the more prominent guidelines, five of six guidelines recommended TCAs and MAOIs as first- or second-line PTSD treatments (Forbes et al. 2010). One

should use caution with these summaries of recommendations because differences exist in the types of TCAs and MAOIs recommended and the level of recommendation. TCAs and MAOIs are usually recommended as second-line treatments in favor of PE, CBT, SSRIs, or SNRIs. Still, TCAs and MAOIs remain good treatment options, especially should patients fail to respond to first-line interventions.

More recently, evidence has emerged in support of newer antidepressants for PTSD treatment, particularly the SNRI venlafaxine (see Friedman et al. 2009 and Rothbaum et al. 2011 for a more in-depth review of newer antidepressants). Two large RCTs found venlafaxine efficacious compared with placebo (Rothbaum et al. 2011), and three of nine guidelines recommend it as first- or second-line PTSD treatment (Stein et al. 2009). Of the more prominent guidelines, only one of seven, ISTSS for adults, recommended venlafaxine (Forbes et al. 2010). However, both the updated VA/DoD and APA guidelines now recommend SNRIs as first-line medications to treat PTSD (Institute of Medicine 2012). Positive findings have also been observed with mirtazapine, a noradrenergic and specific serotonergic and tetracyclic antidepressant, for reducing PTSD over placebo and in reducing nightmares in traumatized populations (Friedman et al. 2009; Rothbaum et al. 2011). Another novel antidepressant, nefazodone, is an effective treatment for PTSD (Rothbaum et al. 2011) and has recommendations in 2 of 11 PTSD practice guidelines (Forbes et al. 2010; Stein et al. 2009). Because nefazodone has serious hepatotoxicity, it is necessary to monitor liver function tests to ensure that this adverse effect does not occur (Friedman et al. 2009). Bupropion, a very effective antidepressant and smoking cessation aid, is a norepinephrine and dopamine reuptake inhibitor. In the single RCT examining its efficacy for PTSD, bupropion showed no superiority relative to placebo and no significant decrease in PTSD symptoms (Becker et al. 2007). Finally, both bupropion and trazodone, another novel antidepressant but of the serotonin agonist and reuptake inhibitor class, are not recommended PTSD treatments because they have fairly weak evidence and have positive findings mostly from clinical observations (Forbes et al. 2010; Institute of Medicine 2012). Because of its strong hypnotic effects, trazodone is recommended as an adjunctive agent for patients with PTSD who have insomnia; because of its serotonergic mechanism of action, it works synergistically with SSRIs or SNRIs. More research is needed with newer antidepressants, but venlafaxine has already been recognized as a first-line treatment.

Other Psychotropics

Evidence for psychotropic drugs other than antidepressants is not very strong, particularly as monotherapy for PTSD (see Friedman et al. 2009 and Rothbaum et al. 2011 for a more in-depth review). Anxiolytics such as alprazolam and clonazepam have not yielded positive results in RCTs, acute interventions in trauma patients, or open-label trials (Rothbaum et al. 2011) and are widely thought to lack PTSD treatment efficacy (Dunlop et al. 2012). Furthermore, the risk-benefit ratio is not favorable for benzodiazepines because of their abuse potential, concerns about sedation in the elderly, and the possibility that they may interfere with the psychological processes needed to benefit from CBT. Therefore, most treatment guidelines recommend against the use of these medications (Forbes et al.

2010; Institute of Medicine 2012; Stein et al. 2009). Although several reviews indicate that anticonvulsants and mood stabilizers such as tiagabine, valproate, and topiramate have not shown evidence for efficacy in RCTs (Friedman et al. 2009; Rothbaum et al. 2011), three studies have found positive results for topiramate (Akuchekian and Amanat 2004; Tucker et al. 2007; Yeh et al. 2011). We mention them here because we are certain that future reviews and meta-analyses will report these findings, especially because topiramate is the first nonantidepressant with demonstrated efficacy for PTSD. At present, however, no major treatment guidelines recommend anticonvulsants or mood stabilizers as monotherapy or as adjunctive medications for PTSD treatment (Forbes et al. 2010; Institute of Medicine 2012; Stein et al. 2009).

Pharmacotherapy Augmentation

Atypical Antipsychotics

There is mixed evidence for the use of AAs as a drug augmentation strategy. It is important to distinguish between the use of AAs for patients with PTSD who have co-occurring psychotic symptoms and their use as adjunctive agents for PTSD among individuals without psychotic symptoms. Frankly, the literature is confusing and sometimes muddled in this regard. Among patients with more severe PTSD who have psychotic symptoms such as auditory and visual hallucinations or paranoid delusions (often related to hypervigilance), adjunctive AAs are a promising approach. We present three main scenarios for the use of AAs in PTSD treatment: as monotherapy, for co-occurring psychotic symptoms, and as adjunctive therapy. It is important to keep these three scenarios in mind because most meta-analyses, including the two referenced in this chapter, have not disentangled the different usages.

Although AAs as monotherapy for PTSD have not been studied extensively, there have been some positive findings. Of the three RCTs of AA monotherapy for PTSD, two studies found significant positive results, one for risperidone and one for quetiapine, relative to placebo (Ahearn et al. 2011; Pae et al. 2008). However, small sample sizes in two of these RCTs and a lack of monotherapy RCTs limit these results.

Another justification for using AAs in PTSD is to treat sometimes co-occurring psychotic symptoms. The two prior reviews did not distinguish between studies of PTSD patients with and without psychotic symptoms in their analyses. Between these two reviews, one RCT of AAs (risperidone) for psychotic PTSD was identified, and although it showed that patients' psychotic symptoms significantly improved, their PTSD symptoms did not (Ahearn et al. 2011). Overall, AA treatment results in PTSD with co-occurring psychotic symptoms are positive but are few and are lacking in RCTs.

Considering AAs as adjunctive therapy for patients who have had a negative or partial response to SSRIs, SNRIs, or other antidepressants complicates the literature. There are a number of small, single-site studies, all done before 2011, suggesting that AAs might be useful as adjunctive treatment for patients who failed to achieve improvement following antidepressant treatment. Both aforementioned reviews suggested that AAs may be particularly useful in reducing intrusive (reexperiencing) and hyperarousal symptoms (Ahearn et al. 2011; Pae et al. 2008), making them a potentially useful adjunct to antidepressant monotherapy. Both meta-analyses of AAs for PTSD, however, are limited because

of their collapsing of adjunctive therapy and monotherapy RCTs. Additionally, Ahearn and colleagues' analyses did not distinguish between open-label trials and RCTs. Still, of the six antidepressant adjunct RCTs analyzed, four showed significantly improved PTSD symptoms relative to placebo (Ahearn et al. 2011; Pae et al. 2008). However, these findings are limited by small sample sizes. In 2011, a large multisite RCT involving 247 veterans and adjunctive risperidone for antidepressant nonresponders or partial responders was published (Krystal et al. 2011). The findings were completely negative. Risperidone was no better than placebo augmentation. As a result, in its 2010 PTSD Clinical Practice Guideline, the VA/DoD, which had recommended adjunctive AA treatment (on the basis of the evidence reviewed above), changed its recommendations so that 1) there is a recommendation against risperidone augmentation and 2) there is no longer any recommendation for adjunctive AA use in the VA/DoD guidelines because it was concluded that evidence favoring all other AAs was inconclusive.

Although in 2009 the ISTSS practice guidelines recommended antipsychotics as adjuncts but not monotherapies, more recent evidence (incorporated into the 2011 VA/DoD guideline) has led to a reversal of this recommendation so that AAs are no longer recommended as either adjunctive therapy or monotherapy for PTSD. In addition, AAs have serious side effects to consider, such as tardive dyskinesia (although rare) and metabolic syndrome (e.g., hyperglycemia, diabetes, heart disease), when weighing the risks and benefits of their use. More monotherapy RCTs are needed before any recommendations can be made for AAs alone. Indeed, the AA literature remains fairly small yet is progressing. Thus, recommendations will change as new data emerge, as did, for example, the VA/DoD's recommendations. For now, there are sufficient data to recommend against using risperidone and a lack of evidence to recommend for or against the use of any other AA.

Antiadrenergics

There are a few controlled studies of antiadrenergic agents (Rothbaum et al. 2011), mostly with negative or inconclusive results. The most encouraging data seem to be for prazosin, a blocker of the α_1 receptors. Prazosin is one of the most well replicated pharmacotherapy augmentation approaches, showing efficacy mostly for reducing nightmares and sleep disruption in PTSD patients (Dunlop et al. 2012) but showing inconsistent results with regard to amelioration of the full PTSD syndrome (Friedman et al. 2009; Rothbaum et al. 2011). Still, prazosin has been specifically recommended for treatment of traumatic nightmares but not for PTSD per se (Forbes et al. 2010; Institute of Medicine 2012).

Despite some favorable anecdotal reports for other antiadrenergics (e.g., the α_2 agonists clonidine and guanfacine), negative RCTs with guanfacine have been reported (Friedman et al. 2009; Rothbaum et al. 2011). No guidelines recommend these medications as efficacious. Indeed, extant trials have yet to prove that guanfacine is useful, much less efficacious, for PTSD (Dunlop et al. 2012).

Thus, prazosin shows the most promise of the antiadrenergics but as an adjunctive medication to help reduce problems with sleep and nightmares, a common reexperiencing and intrusion symptom for PTSD patients. There are a number of ongoing large RCTs with prazosin that may yet demonstrate its efficacy for the full PTSD syndrome.

Emerging Treatments

Despite evidence for such first-line PTSD treatments as PE, trauma-focused CBT, and SSRIs, many patients do not respond to these therapies. Indeed, 33% of psychotherapy patients still meet diagnostic criteria for PTSD posttreatment (Bradley et al. 2005), and 40% of pharmacotherapy patients do not respond to treatment (Stein et al. 2006). Innovative alternatives to current first-line treatments are clearly needed. In the following section, we review several novel, promising treatments, focusing on medication-enhanced psychotherapy, early interventions, alternative delivery methods, and complementary and alternative medicine. Although these newer approaches are not all strongly supported by RCTs, emerging evidence supports their potential use for alleviating and perhaps preventing PTSD.

Medication-Enhanced Psychotherapy

MEP involves the use of a drug to improve the efficacy of therapy, with the drug typically added to PE. Several medications are currently being tested, but MEP strategies tend to utilize drugs that either act directly on PTSD symptoms, aiming for an additive effect, or boost the learning process during therapy, aiming for a facilitative effect. For the former, the most common MEP approach is SSRI-augmented PE. Three RCTs of combined SSRI and PE therapy have shown mixed results. In the first published RCT of SSRI-augmented PE (Rothbaum et al. 2006), 88 patients with PTSD were treated with open-label sertraline and then were assigned to continued sertraline alone or with PE. Although the sertraline alone was not associated with further improvement, the PE augmentation led to additional reduction of PTSD symptoms to medication partial responders. In a mirror design, Simon and colleagues (2008) first gave 23 participants eight sessions of PE and then paroxetine or placebo while continuing PE to patients who were still symptomatic. Paroxetine augmentation did not significantly reduce PTSD symptoms or increase response relative to placebo, suggesting that medications do not boost psychotherapy effects. However, Schneier and colleagues (2012), in their RCT of 37 survivors of the 9/11 World Trade Center attacks, demonstrated that paroxetine and PE administered together reduced PTSD symptoms significantly more than PE plus placebo, with significantly more treatment responders achieving clinical remission. PE was discontinued after 10 weeks, revealing no differences between paroxetine and placebo in PTSD symptom reduction and the number of treatment responders and remitters. Thus, despite equivocal results for SSRI-augmented PE, the combined approach of treating patients with an SSRI and PE simultaneously seems promising. Future research should continue to investigate the effects of combined psychotherapy and pharmacotherapy and other combinations.

Unlike SSRI-augmented PE, cognitive enhancers do not directly treat symptoms. Instead, these adjunctive medications seek to make psychotherapy more effective. Currently, the most well studied cognitive enhancer is D-cycloserine (DCS), an *N*-methyl-D-aspartate (NMDA) partial agonist. DCS is thought to be useful for facilitating ET because it improves glutamate activity at NMDA receptors that mediate intracellular learning processes involved in cell change, thereby facilitating extinction learning and the consolidation of new fear memories (Burton et al., in press). There is good general ev-

idence for DCS in MEP of ET for anxiety disorders (Kearns and Rothbaum 2012) but mixed results for DCS with CBT for PTSD (Burton et al., in press). Although there are seven active studies investigating DCS with PE for PTSD (Dunlop et al. 2012), there are just two relevant published RCTs. Treating 67 mixed trauma survivors, de Kleine and colleagues (2012) compared DCS and PE with placebo and PE, finding both groups equally efficacious in reducing PTSD symptoms. DCS patients, however, were more likely to show treatment response. Of further note, patients with more severe PTSD who required more treatment sessions responded significantly better to DCS than placebo at the end of treatment and at follow-up. On the other hand, an RCT of 26 veterans with PTSD (Litz et al. 2012) found that PE plus DCS patients did significantly worse than PE plus placebo patients, which is difficult to explain. Although more research on DCS as MEP for PTSD is needed, initial findings suggest that DCS does not generally enhance PE over placebo, but it may help certain groups of patients, such as those with higher pretreatment PTSD symptoms who may benefit from a longer course of treatment (de Kleine et al. 2012).

Although SSRIs and DCS are the most commonly studied MEP approaches, there are four other ongoing cognitive enhancer trials with PTSD (Dunlop et al. 2012). Both hydrocortisone and yohimbine enhance extinction learning in part through their effects on norepinephrine, and methylene blue enhances signal transport to mitochondria, boosting protein transcription vital for synapse strengthening (Dunlop et al. 2012). Hydrocortisone, a glucocorticoid, may augment memory formation and fear extinction by acting on the cyclic adenosine monophosphate/protein kinase A signaling cascade and glucocorticoid receptors that signal to the amygdala (Dunlop et al. 2012). Although no clinical data exist for these medications with PTSD, the medications have shown promise in extinction training in both animals and humans. Future research may also want to directly compare these medications and investigate if they differentially benefit certain groups of patients.

Last, the use of methylenedioxymethamphetamine (MDMA or ecstasy) to facilitate the patient's immersion into therapy represents an interesting exception to the aforementioned MEP strategies. MDMA's serotonin boost and resulting increased emotion, disinhibition, empathy, and euphoria are thought to make the patient more willing to actively engage in the intense exposure therapy experience (Dunlop et al. 2012). Despite 83% of MDMA MEP patients responding to treatment in the first RCT of MDMA plus psychotherapy for PTSD (Mithoefer et al. 2011), this finding is likely confounded by expectancy bias because the observable effects of MDMA are highly salient (Dunlop et al. 2012). Additionally, patients had to be closely monitored by highly trained staff, making effectiveness outside the lab setting unlikely. In addition to methodological problems with this research, there is also concern about the potential neurotoxicity of MDMA. However, the results remain encouraging because the patients were refractory to previous therapy, and indeed, three MDMA MEP trials are ongoing (Dunlop et al. 2012).

Early Interventions

It is essential to emphasize that exposure to traumatic events is not uncommon (Breslau 2009). Furthermore, although almost everyone is upset immediately after exposure to a traumatic event, most

will not progress to acute stress disorder (ASD), PTSD, or some other clinical diagnosis. Therefore, acute interventions are not "treatments" per se but preventive measures to facilitate emotional recovery from traumatic exposure and to prevent the later onset of ASD, PTSD, etc. These interventions presuppose that most people are resilient and likely to recover, and the goal is to facilitate that recovery while identifying the minority who may develop clinical problems that require clinical treatment.

With the DSM-5 stipulation that PTSD cannot be diagnosed until at least 1 month has passed after exposure to the traumatic event, it is difficult to demonstrate the effectiveness of early interventions because most trauma survivors' symptoms will diminish within the first month following exposure (Rothbaum et al. 1992). Thus, early interventions should either be targeted to patients most at risk for PTSD development or be tolerable to all trauma survivors such that those who would naturally recover are not harmed by preventive strategies. Despite the failures of psychological debriefing (PD), there is encouraging new evidence for approaches to prevent PTSD.

Psychological Debriefing

Although PD is not a novel concept, research on its efficacy and use is fairly new. A review of major RCTs and of previous critical reviews indicate that PD is ineffective and possibly harmful (Kearns et al. 2012). Specifically, Kearns and colleagues (2012) note that some patients in three different studies who received debriefing actually had worse PTSD symptoms than control groups. The group delivery of PD, the one-time intervention, and its nontherapeutic reexposure to traumatic memories likely explain these results. Consequently, the major PTSD treatment guidelines do not recommend PD as an initial prevention effort (Forbes et al. 2010). Psychological first aid (PFA), another early approach, is evidence informed, although it lacks rigorous scientific evidence for its efficacy as a treatment program (Fox et al. 2012). PFA aims to help trauma victims with initial needs and, unlike PD, does not involve the emotional processing that may be problematic.

Psychotherapy-Based Early Interventions

Beyond PD and PFA, there are other promising psychological interventions that have utilized cognitive techniques and therapeutic exposures or have been better targeted. A myriad of brief early interventions such as traumatic memory organization, self-help and psychoeducation, and stepped collaborative care have been shown to help patients cope with their posttraumatic reactions while providing resources for seeking future PTSD care (Kearns et al. 2012). Interventions targeted at specific trauma populations, namely, combat and sexual assault survivors, seek to normalize trauma reactions and provide coping strategies; they have shown promising results in these often difficult to treat populations (Kearns et al. 2012).

Until recently, there were no controlled trials of an exposure-based intervention delivered in the immediate aftermath of a trauma. In fact, some researchers have cautioned against intervening too early with all trauma survivors (Bryant 2011), but there is emerging evidence to the contrary. Rothbaum and colleagues (2012) conducted an intervention with traumatized emergency room patients who endorsed criterion A for PTSD, comparing a brief PE protocol to an assessment-only

condition. This is the earliest known psychotherapy PTSD intervention to date, with patients enrolled in the study and starting their first treatment session on average within 12 hours after hospital arrival (median 6 hours). Intervention patients had significantly less severe depression and PTSD symptoms 1 month posttrauma, when PTSD could first be diagnosed, as well as fewer PTSD symptoms 3 months posttrauma than assessment-only patients. At 3 months posttrauma, when PTSD can be considered chronic, patients who received the intervention had half the rate of PTSD than patients who received only assessment without exposure. Furthermore, the fact that intervention patients who may have naturally recovered were not made worse lends support to the argument that it may be safe to administer exposure therapy to all trauma survivors.

Several other studies have tested nonacute CBT interventions. These interventions are not initiated until usually at least 10–14 days (sometimes not until at least 1 month) after the trauma, often with individuals meeting ASD diagnostic criteria (Kearns et al. 2012). Although these early CBT interventions have not been thoroughly studied in veterans or military combat populations, these trials have included an array of trauma survivors, from assault to sexual assault to motor vehicle accidents. Overall, Kearns and colleagues (2012), in their review, reported positive results from at least 10 studies in terms of better PTSD symptom outcomes due to early CBT-based interventions, noting that exposure techniques are likely key to these results. Variations on the design of early interventions such as timing, dosage, population (e.g., combat versus sexual versus motor vehicle trauma), targeting at-risk patients, and type of intervention ought to be pursued to determine who needs preventive care most and which interventions work best with different patients. Still, these findings are exciting and, from a public health perspective, have the potential to alleviate PTSD's societal toll before the disorder can fully develop.

Pharmacotherapy-Based Early Interventions

There is some evidence for preventive effects in several medications, though they are less rigorously studied than early psychological interventions. Beta blockers, namely, propranolol, have been studied somewhat extensively as several reports and smaller studies have noted propranolol's capacity to reduce intrusive recollections, general arousal, and physiological reactivity (Rothbaum et al. 2011), but it has not been shown to prevent the development of PTSD (Dunlop et al. 2012). Indeed, RCTs comparing propranolol to placebo as an early intervention found that it reduced arousal but did not prevent PTSD (Kearns et al. 2012). Other medications such as hydrocortisone, ketamine, and morphine have shown some associations with favorable changes, but more research is needed (Kearns and Rothbaum 2012; Kearns et al. 2012). Of these three medications, hydrocortisone has the most demonstrated efficacy in more rigorously designed studies. Three controlled trials (two randomized) of stress doses of hydrocortisone in cardiac surgery and septic shock patients compared with placebo or standard care groups indicated that stress dose hydrocortisone patients had significantly less severe PTSD symptoms and less likelihood of developing PTSD relative to controls (Schelling et al. 2006). Morphine has also shown preventive potential, as a retrospective study of Iraq

war veterans found that morphine administration during trauma care was associated with a reduced risk for PTSD development (Holbrook et al. 2010). Although this exciting finding is limited by its correlational, retrospective design, it still warrants further investigation of morphine as a protective factor against PTSD through more rigorous studies such as controlled trials. In summary, the evidence on early pharmacological interventions for PTSD remains inconclusive, and these medications are not generally recommended for PTSD treatment. Glucocorticoids show the most promise as an early pharmacological intervention.

Alternative Delivery Methods

Typically, psychotherapy sessions for PTSD are conducted in person, individually. The need for more tolerable and accessible treatments has spurred innovation in treatment delivery. Specifically, nonindividualized psychotherapy is being increasingly offered and studied, and technological advances are increasing the accessibility of treatment, both group and individual.

Despite the rationale for couples, family, or group therapy because of PTSD's significant impact on relationships, there are limited efficacy data (Kearns and Rothbaum 2012) and no first- or second-level recommendations for group or nonindividualized therapy (Forbes et al. 2010; Institute of Medicine 2012). Two better designed studies of group interpersonal therapy for mixed trauma survivors showed promise for improving depression and PTSD symptoms, although not always significantly (Kearns and Rothbaum 2012). The positive findings have been limited to mostly veteran populations and are limited by small sample sizes and nonexperimental designs such as case studies and nonrandomized trials, although a recent study did find cognitive-behavioral couples therapy efficacious (Kearns and Rothbaum 2012; Monson et al. 2012). On the other hand, a large group therapy RCT of 360 veterans revealed negative results, with no differences in PTSD improvement or any other outcomes between trauma-focused group therapy and present-centered group therapy, although PTSD symptoms significantly improved from baseline within each treatment type (Schnurr et al. 2003). Although more research is certainly needed, the rationale for group or couples therapy is especially strong for the military population because many returning veterans report feeling out of place or misunderstood (Cukor et al. 2009). Thus, activating engagement with a veteran's family or spouse represents a logical starting point for helping him or her return back to civilian life, although this is not recommended in the IOM report (Institute of Medicine 2008).

Virtual Reality

Many PTSD patients feel emotionally disengaged and are unable to process or confront their traumatic experience, leading to treatment failures and dropouts (Cukor et al. 2009). Virtual reality exposure (VRE) aims to overcome these obstacles by introducing sensory cues to augment the patient's imagination (Burton et al., in press). It is important to note that VRE is not a unique treatment but rather a unique treatment delivery approach specific to PE. Essentially, VRE uses virtual environments that provide visual, auditory, and olfactory stimuli; allow patients to move at their own pace; and provide a customizable experience. In turn, VRE's features help patients en-

gage with their emotions, habituate to the traumatic fear memory and stimuli, and process their experience. Still, there is a paucity of efficacy data for PTSD from large, rigorous RCTs, with most of the evidence coming from small, uncontrolled pilot studies and case reports (Kearns and Rothbaum 2012). However, the lone published RCT showed significant PTSD symptom reduction in the VRE patients (Difede et al. 2007), consistent with the positive findings from most of the other case reports, pilot studies, and uncontrolled trials (Burton et al., in press; Cukor et al. 2009; Kearns and Rothbaum 2012; Ressler and Rothbaum 2009). Likely because of this lack of evidence from rigorously designed studies, the major PTSD treatment guidelines do not yet recommend VRE (Institute of Medicine 2012), although existing evidence is promising. Although innovative, VRE is not without its limitations because it is a delivery method unique to PE, cannot be customized to every kind of traumatic event, and has mostly been utilized in veteran populations. For example, a virtual Iraq VRE program for Iraq war veterans is currently being investigated, but this treatment would be relevant to that specific population only and cannot fully customize to the patient's combat trauma. There are several ongoing RCTs of VRE, including a multisite 2 × 2 study of VRE and PE augmented with DCS or placebo, which will hopefully provide better insight into VRE's efficacy for military-related PTSD.

Telemedicine

Investigations of telemedicine, videoconferencing between patient and therapist, suggest preliminary support for its use in treating PTSD (Cukor et al. 2009). A pilot randomized trial of group-delivered CBT via telemedicine found telemedicine equally effective as group therapy in person (Frueh et al. 2007). Despite numerous studies on telemedicine-delivered CBT for PTSD and anxiety disorders, to our knowledge there are just two published studies examining PE delivered via telemedicine (Gros et al. 2011; Tuerk et al. 2010). In both studies, PE delivered individually via telemedicine led to statistically and clinically significant reductions in PTSD and depression symptoms with large effect sizes. All patients offered telemedicine accepted the treatment, and no issues with patient safety emerged in either study. Recent pilot data from the first RCT for group CPT delivered via telemedicine show it to be feasible and efficacious, as fewer participants dropped out than usual in veteran or PTSD populations, and telemedicine patients exhibited reductions in PTSD symptoms that were both clinically significant and not significantly different from in-person patients (Morland et al. 2011). Thus, these few studies suggest efficacy for telemedicine-delivered psychotherapy in both group and individual settings. More replication of results is required before recommending telemedicine, but the VA currently offers telemedicine services in many of its clinics. Indeed, telemedicine is promising because it can alleviate such treatment barriers as stigma, cost, and geography.

Internet Cognitive-Behavioral Therapy

Another approach to reducing barriers to treatment, Internet cognitive-behavioral therapy (ICBT) utilizes an online protocol in which patients learn rationale for treatment, practice cognitive restructuring or behavioral exercises, and complete in vivo exposure homework assignments. Reviews of the few extant

controlled trials of ICBT noted two main protocols: DE-STRESS, specifically for military populations, and Interapy (see Cukor et al. 2009 and Kearns and Rothbaum 2012 for a more in-depth review). These two treatments both utilized exposure and cognitive techniques, with positive results of treatment groups achieving significant PTSD symptom decreases at follow-up (Cukor et al. 2009; Kearns and Rothbaum 2012). Generally, there is more extensive support for the use of ICBT in other anxiety disorders because PTSD is often more difficult to treat. With more research to bolster the few positive findings, ICBT is a potentially strong alternative method that may better reach PTSD patients.

Complementary and Alternative Medicine

Because of the imperfections of even first-line treatments and the need for more mental health care options, CAM approaches are highly sought after, even among veterans, and are popular to study, with at least 438 unpublished ongoing or completed trials (Strauss et al. 2011). In response to the rising popularity of CAM treatments, Strauss and colleagues (2011) reviewed the RCTs of CAM for PTSD, finding most of the studies of poor quality commonly because of such limitations as low power, unexplained missing data, and a lack of intent-to-treat analyses. Studies of meditation yield some positive results, suggesting that meditation may be superior to control or psychotherapy, but design flaws limit these findings (Strauss et al. 2011). Recent studies have also shown improvements in PTSD symptoms for meditation, but again, these were flawed designs because they lacked control groups (Strauss and Lang 2012). Two reviews of emerging treatments note the presence of one promising study of acupuncture, which found that it significantly reduced PTSD symptoms and was superior to wait-list control and equal to group CBT (Cukor et al. 2009; Strauss et al. 2011). This study had a strong design, and further research replicating this study appears warranted. As previously mentioned, relaxation is part of the PE protocol, but studies have also examined these techniques as monotherapy. Although three RCTs have shown some positive effects on PTSD symptoms from relaxation and similar efficacy to other treatments, these studies were underpowered and had unclear randomization and blinding procedures (Strauss et al. 2011). However, several studies that modestly improved PTSD symptoms were excluded from the CAM review (Strauss et al. 2011), suggesting that relaxation has a place in PTSD treatment but not as a monotherapy. Finally, there is a dearth of data on other popular CAM approaches such as yoga (Cukor et al. 2009) and service animals such as dogs or horses. There has been a call from the government for research specifically on PTSD service dogs because nearly all of the evidence is anecdotal. Ultimately, although CAM treatments lack hard evidence of efficacy, their rationale is appealing, and better designed, more rigorous studies like RCTs could support their utility

Conclusion

Certainly, there is no scarcity of PTSD treatment efficacy research. However, the evidence is spread thin among a wide array of treatments, with the exception of PE; CPT; trauma-focused CBT; and antidepressants, SSRIs and SNRIs in particular. Overall, consistent with all of the guidelines, we recommend PE and CPT as the first-line treatments for PTSD be-

cause they simply have the most rigorous evidence supporting their efficacy, although EMDR and other forms of trauma-focused CBT appear to be equally effective (Bradley et al. 2005). In contrast to the IOM guidelines (Institute of Medicine 2008) and in line with most other treatment guidelines, we see SSRIs and SNRIs as being effective treatments, as attested by numerous guidelines and the most rigorous pharmacotherapy meta-analysis (Stein et al. 2006) and recommend them as first-line pharmacological treatment. Given that PE, CPT, and other CBT approaches can be difficult and not all patients may be willing to accept psychotherapy, SSRIs and SNRIs should be recognized as an evidence-based alternative.

In terms of the most promising research areas, DCS, technologically based delivery alternatives, and early psychological interventions have yielded exciting initial results. DCS may speed up the fear extinction process and boost therapy gains for patients with more severe PTSD. VRE, telemedicine, and ICBT could expand CBT and PE to more patients, helping to disseminate these first-line recommended treatments. Although early interventions are still highly debated in the field, clearly they have shown positive results on abandoning PD, and the sheer significance of their potential to prevent PTSD and its toll on society further warrant their continued study.

Finally, there are several research areas with great promise that are severely lacking good evidence for PTSD treatment efficacy. The alternative delivery methods of ICBT and group, family, or couples therapy have few trials and even fewer RCTs, yet they are feasible and rational treatment approaches that could overcome the stigma surrounding PTSD, especially among military personnel. Emotion-based therapies such as ACT and DBT have shown strong promise in other anxiety disorders and borderline personality disorder, respectively, but require RCTs with PTSD patients. Both ACT and DBT share some similar theoretical basis with CBT and could be a useful alternative to those patients less willing to participate in PE or take medications. Although CAM treatments do not demonstrate much promise as monotherapy, they could be very useful as adjunctive treatment or as self-care outside of a primary treatment such as CBT, PE, or SSRIs, as described in the PE protocol. More RCTs of CAM therapies could yield better evidence for their efficacy to treat PTSD, and much more extensive research with them is necessary.

Although a PTSD diagnosis is an unfortunate situation for a patient, the proliferation of treatment efficacy research in the field has provided us with good treatments that work and exciting, emerging treatments that may be good alternatives in the future. We have attempted as comprehensive of a review as possible given our limitations and goal of remaining concise. We hope that this review helps to better synthesize the PTSD treatment literature that is ever growing and evolving.

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CHAPTER 28

Acute Stress Disorder

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Acute stress disorder (ASD) was introduced in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders,* DSM-IV (American Psychiatric Association 1994). The purpose of this diagnosis was to describe severe posttraumatic stress responses within the first month following a trauma and also to identify individuals at risk of developing chronic posttraumatic stress disorder (PTSD) following exposure to a traumatic event (Koopman et al. 1995). The need to have a separate diagnosis describing initial PTSD was recognized because one cannot formally diagnose PTSD within a month of trauma exposure. There was concern that severe stress reactions were not being adequately addressed because they were not diagnosed. Accordingly, the diagnosis was introduced with criteria that largely resembled PTSD criteria, with the exception that considerable emphasis was placed on dissociative symptoms as an additional cluster (Harvey and Bryant 2002). The introduction of this new diagnosis led to an unprecedented level of research on early interventions for PTSD reactions occurring in the initial weeks following trauma exposure. In this chapter I provide an overview of the current evidence for treating ASD and potential changes to understanding this evidence in light of marked changes to the diagnostic criteria in DSM-5 (American Psychiatric Association 2013).

Rationale for Treating ASD

It is important to understand that treatment studies of ASD have typically attempted to achieve targeted secondary prevention insofar as the goal has been to limit development of chronic PTSD. The advancement achieved by ASD diagnosis in early intervention studies was that it provided the means to target acutely traumatized people who were apparently at high risk for PTSD rather than applying the commonly adopted approach of global counseling for all trauma survivors; the latter approach has failed to reduce

subsequent rates of PTSD (for a review, see McNally et al. 2003). Since the introduction of the ASD diagnosis, many studies have assessed ASD within a month of the trauma exposure and subsequently followed patients up at variable times to determine the extent to which initial ASD predicts chronic PTSD. Overall, studies find that a significant proportion of patients with ASD do subsequently have PTSD; however, most patients who eventually develop PTSD do not meet initial criteria for ASD (Bryant 2011). Although this has raised some concerns about the overall utility of the ASD diagnosis, it nonetheless validates the merit of attempting to prevent PTSD in these patients because many of them will be on a trajectory for chronic PTSD.

Psychotherapy Approaches

The treatment for ASD that enjoys the strongest degree of support is trauma-focused cognitive-behavioral therapy (CBT). It is the recommended treatment across a number of treatment guidelines (Foa et al. 2009; Forbes et al. 2007). This modality usually commences with psychoeducation about the trauma responses and then focuses on three major strategies: anxiety management, exposure, and cognitive restructuring. Psychoeducation informs the patient about common symptoms following a traumatic event and discusses the way in which the core symptoms will be treated during the course of therapy. Anxiety management aims to reduce anxiety through a range of techniques that may include breathing retraining, relaxation skills, and self-talk. Exposure therapy usually involves both imaginal and in vivo exposure. Imaginal exposure requires the patient to vividly imagine his or her traumatic experience for prolonged periods, usually for at least 30 minutes. The therapist asks the patient to provide a narrative of the traumatic experience in a way that emphasizes all relevant details, including sensory cues and affective responses. In vivo exposure involves graded exposure to feared stimuli in which the patient is asked to remain in close proximity to mildly fearful reminders of the trauma and then repeating this exercise with increasingly fearful situations until the patient feels comfortable with most reminders of the experience. Cognitive restructuring involves teaching patients to identify and evaluate the evidence for negative automatic thoughts as well as helping patients to evaluate their beliefs about the trauma, the self, the world, and the future. There is overwhelming evidence for the efficacy of CBT in reducing the severity of chronic PTSD reactions (Cahill et al. 2009).

Most models of CBT have developed from fear conditioning as a core construct in the development and resolution of posttraumatic stress. This model posits that cues present during a traumatic event are paired with strong fear reactions, leading to conditioned fear responses that activate fear networks when the individual encounters these stimuli in another setting (Foa et al. 1989). It is argued that the strong fear elicited by the trauma will lead to strong associative conditioning between the fear and the events surrounding the trauma (Milad et al. 2006). As reminders of the trauma occur (conditioned stimuli), people then respond with fear reactions (conditioned response). This model proposes that successful recovery from trauma involves extinction learning, in which repeated exposure to trauma reminders or memories results in new learning that these reminders no longer signal threat (Davis and Myers 2002).

More cognitively oriented models emphasize that appraisals of the traumatic event and associated symptoms are the key etiological and maintaining factors, and accordingly, these approaches tend to emphasize cognitive elements of CBT (Ehlers and Clark 2000). This perspective is supported by evidence that people with ASD exaggerate both the probability of future negative events occurring and the adverse effects of these events (Warda and Bryant 1998). Moreover, ASD participants display cognitive biases for a broad array of events beyond those directly related to the traumatic experience, including external harm, somatic sensations, and social concerns (Smith and Bryant 2000). Experimental studies indicate that individuals with ASD respond to a hyperventilation task with more dysfunctional interpretations about their reactions than individuals without ASD (Nixon and Bryant 2005). From a predictive perspective, catastrophic appraisals about oneself in the period after trauma exposure predict subsequent PTSD (Ehlers et al. 1998).

Psychotherapy for ASD: Review of the Evidence

Over the last few decades, researchers have attempted to limit subsequent PTSD by adapting CBT approaches to people shortly after trauma exposure. Although these attempts showed some promise for secondary prevention, they were limited by various methodological issues (Brom et al. 1993; Kilpatrick and Veronen 1983). One challenge facing this research was that earlier studies admitted trauma survivors displaying elevated levels of distress; this can be problematic because the natural remission from initial stress reactions potentially confounds the effects of early intervention and natural recovery (Bryant 2003). For example, Foa and colleagues provided brief CBT to sexual and nonsexual assault victims shortly after assault (Foa et al. 1995). This study (nonrandomly) allocated participants to either CBT (including exposure, anxiety management, in vivo exposure, and cognitive restructuring) or a condition involving repeated assessments. Each participant received four treatment sessions and then received assessment by blind assessors at 2 months posttreatment and 5 months follow-up. Whereas 10% of the CBT group met criteria for PTSD at 2 months, 70% of the control group met criteria; there were no differences between groups at 5 months, although the CBT group was less depressed. One implication of this study is that CBT may accelerate natural recovery from trauma. In a subsequent study, Foa et al. (2006) randomly allocated survivors of assault who met criteria for acute PTSD in the initial weeks after the assault to four weekly sessions of CBT, repeated assessment, or supportive counseling (SC). At posttreatment, patients in the CBT and repeated-assessment conditions showed comparable improvements. SC was associated with greater PTSD severity and greater general anxiety than the CBT group. At 9-month follow-up, approximately 30% of participants in each group met criteria for PTSD. Again, this study may not have found a relative advantage in early provision of CBT because of the focus on patients with PTSD rather than patients with ASD.

In an attempt to focus early intervention on those recently trauma-exposed people who are more likely to not remit, subsequent studies focused on treating patients who met criteria for ASD. In an initial pilot study, Bryant and colleagues randomly allocated motor vehicle accident or nonsexual assault survivors with ASD to either CBT or SC (Bryant et al. 1998). Both interventions consisted of five

1.5-hour weekly individual therapy sessions. CBT included education about posttraumatic reactions, relaxation training, cognitive restructuring, and imaginal and in vivo exposure to the traumatic event. The supportive counseling condition included trauma education and more general problem-solving skills training in the context of an unconditionally supportive relationship. At the 6-month follow-up, there were fewer participants in the CBT group (20%) who met diagnostic criteria for PTSD compared with supportive counseling control participants (67%). In a subsequent study that dismantled the components of CBT, 45 civilian trauma survivors with ASD were randomly allocated to five sessions of either 1) CBT (prolonged exposure, cognitive therapy, and anxiety management), 2) prolonged exposure combined with cognitive therapy, or 3) supportive counseling (Bryant et al. 1999). This study found that at 6-month follow-up, PTSD was observed in approximately 20% of both active treatment groups compared with 67% of those receiving supportive counseling. A follow-up of participants who completed these two treatment studies indicated that the treatment gains of those who received CBT were maintained 4 years after treatment (Bryant et al. 2003b).

Three other studies by the same research group have supported the efficacy of CBT for people with ASD. One study randomly allocated civilian trauma survivors (N=89) with ASD to either CBT, CBT associated with hypnosis, or supportive counseling (Bryant et al. 2005). This study added hypnosis to CBT because it has been suggested that hypnosis may facilitate the emotional processing that can be impeded by the dissociative symptoms that characterize ASD (Spiegel et al. 1996). Accordingly, the hypnosis was provided immediately prior to imaginal exposure in an attempt to facilitate emotional processing of the trauma memories. In terms of treatment completers, more participants in the supportive counseling condition (57%) met PTSD criteria at 6-month follow-up than in the CBT (21%) or CBT plus hypnosis (22%) conditions. Interestingly, participants in the CBT plus hypnosis condition reported greater reduction of reexperiencing symptoms at posttreatment than those in the CBT condition. This finding suggests that hypnosis may facilitate treatment gains in participants with ASD. Another recent study replicated the original Bryant et al. (1998) study with a sample of participants with ASD (N=24) who sustained mild traumatic brain injury following motor vehicle accidents (Bryant et al. 2003a). This study investigated the efficacy of CBT in people who lost consciousness during the trauma as a result of their traumatic injury because it is possible that this impaired memory of the trauma may result in different treatment outcomes (Bryant 2001). Consistent with the previous studies, fewer participants receiving CBT (8%) met criteria for PTSD at 6-month follow-up than those receiving supportive counseling (58%). In the largest study to date, 90 trauma survivors were assigned to receive five weekly sessions of either 1) imaginal and in vivo exposure, 2) cognitive restructuring, or 3) assessment only (Bryant et al. 2008). Findings indicated that exposure therapy was associated with lower levels of PTSD, depression, and anxiety at posttreatment and follow-up compared with patients in the other conditions.

Importantly, other centers have also utilized CBT for early intervention and demonstrated efficacious results. In an Israeli study of early versus later intervention, Shalev and colleagues randomly assigned 242 patients admitted

to an emergency department who met criteria for either full or subsyndromal ASD to either prolonged exposure, cognitive restructuring, wait list (those patients were then randomly assigned to exposure or cognitive restructuring after 12 weeks), escitalopram (a selective serotonin reuptake inhibitor [SSRI]), or placebo (Shalev et al. 2012). At 9-month follow-up, PTSD rates were comparable across exposure (21%) and restructuring (22%) conditions, relative to the much higher rates in the SSRI (42%) and placebo (47%) conditions. Interestingly, there were no longer-term differences between participants who received the early or later provision of CBT.

Several other controlled trials that have applied CBT to acute PTSD have recruited patients within months of the trauma, with mixed results. In the United Kingdom, Bisson and colleagues randomly assigned 152 traumatic injury survivors to receive four sessions of CBT or no intervention 1–3 weeks after the trauma (Bisson et al. 2004). They found that the intervention group evidenced lower PTSD symptoms at 13 months, although there were no group differences in anxiety or depression. Although this approach focused on severe acute PTSD symptoms rather than DSM-IV criteria for ASD, it nonetheless found a significant relative improvement. One Dutch study randomly assigned 143 patients with acute PTSD within 3 months of trauma exposure to either four sessions of CBT or wait list (Sijbrandij et al. 2007). Although CBT led to greater PTSD reduction after treatment, this difference was no longer significant at a 4-month follow-up. Using a different design, a UK study required acute trauma survivors to complete a 3-week self-monitoring phase prior to enrolling in a formal CBT trial in an attempt to reduce the likelihood that those commencing treatment would remit on their own (Ehlers et al. 2003). Those patients who still had PTSD at the end of this phase were randomly assigned to either up to 12 weekly sessions of CBT; a self-help condition (one session with a clinician and a self-help booklet); or repeated, but infrequent, assessments of PTSD symptoms. This CBT program emphasized cognitive therapy rather than prolonged imaginal exposure to traumatic memories. CBT was superior to the self-help condition and repeated assessment on measures of PTSD at posttreatment and at follow-up.

Other approaches have used brief CBT in the acute setting but have not adopted a formal ASD or PTSD entry criterion. One study provided two sessions of CBT intended to promote adaptive memory reconstruction in 17 survivors of accidents (Gidron et al. 2001). This approach was based on the premise that facilitating people's organization of trauma memories would assist with processing of these memories, thereby assisting recovery (Ehlers and Clark 2000). The study used an entry criterion of a heart rate higher than 94 beats per minute at admission to the emergency room because of evidence that this is predictive of subsequent PTSD (see Bryant et al. 2000; Shalev et al. 1998). This study, which provided telephone-administered CBT 1–3 days after the accident, found that patients who received CBT had greater reductions in severity of PTSD symptoms 3–4 months after the trauma than did those who received two sessions of supportive listening. A more recent study recruited patients admitted to the emergency room following trauma and randomly assigned 137 patients to receive three sessions of prolonged exposure or an assessment control condition (Rothbaum et al. 2012). Exposure commenced in the emergency room and was

repeated 1 and 2 weeks following the initial session. Patients who received the exposure treatment had significantly lower PTSD scores 12 weeks following the injury relative to those who received the assessment alone. This study demonstrates the safety of commencing exposure very soon after trauma exposure, although it is difficult to determine the extent to which the initial or later exposure sessions were instrumental in achieving treatment gains.

In another study, 40 recent trauma victims who met criteria for ASD were administered three sessions of therapy: all participants received psychoeducation and progressive relaxation, and half of the participants were also randomly allocated to receive either exposure or supportive counseling in addition (Freyth et al. 2010). Both groups displayed comparable symptom reduction 4 years after treatment. Following treatment, participants in the exposure condition displayed attenuated heart rate in response to trauma cues, whereas those receiving supportive counseling displayed a marginal increase in heart rate.

In a rare study of ASD in children, 30 children with ASD who were survivors of assault were randomly allocated to either cognitive processing therapy or supportive counseling (Nixon 2012). Cognitive processing therapy is a form of CBT that requires participants to write about their traumatic experience and then places substantial emphasis on correcting maladaptive appraisals that participants have about the experience and their capacity to manage it (Resick and Schnicke 1992). There is strong evidence for this approach in the context of chronic PTSD (Resick et al. 2002, 2008). This study of children found that at both posttreatment and 6-month follow-up both interventions were comparably effective. Although this result needs to be considered in the context of the very small sample size, it nonetheless raises the possibility that the findings reported in adult studies may not be generalizable to children. It is possible that children are less capable of using the cognitively oriented cognitive processing therapy or possibly that supportive counseling is relatively effective in this younger age group.

Summarizing the evidence for early intervention, one meta-analysis of four studies of CBT for ASD relative to supportive counseling reported that the relative risk for a PTSD diagnosis was 0.36 (95% confidence interval=0.17–0.78), supporting the evidence for the utility of brief CBT for ASD (Kornør et al. 2008). This finding accords with another meta-analysis that focused on a larger range of studies of early intervention, including studies with patients meeting criteria for ASD or acute PTSD (Roberts et al. 2009).

Pharmacological Approaches

Very few controlled trials have been undertaken to examine the efficacy of psychopharmacological interventions in treating symptoms of ASD. In the study described in the previous section, Shalev randomly assigned 242 patients admitted through an emergency room meeting criteria for either full or subsyndromal ASD to either prolonged exposure, cognitive restructuring, wait list (those patients were then randomly assigned to exposure or cognitive restructuring after 12 weeks), escitalopram (an SSRI), or placebo (Shalev et al. 2012). At 9-month follow-up, PTSD rates in both exposure (21%) and restructuring (22%) conditions were lower than rates in the SSRI (42%) and placebo (47%) conditions. These findings from the

largest and mostly tightly controlled study indicate that 1) escitalopram does not perform markedly better than placebo and 2) SSRIs (which have traditionally been used to treat PTSD) may not have substantial gains for patients displaying ASD symptoms.

Other studies have attempted to achieve secondary prevention by using pharmacological interventions that have been applied to chronic PTSD. One case series of three patients found that tricyclic antidepressant medications were effective in reducing symptoms of ASD (Blake 1986). A randomized trial found that 7 days of treatment with imipramine was more effective in treating symptoms of ASD in 25 child and adolescent burn victims than chloral hydrate (Robert et al. 1999). In another case study, a benzodiazepine, temazepam, was administered within 1–2 weeks of the trauma to four trauma survivors over a period of 5 nights, then was tapered for 2 nights before being discontinued (Mellman et al. 1998); temazepam was associated with reduced sleep difficulties and PTSD severity. Another study treated 13 trauma survivors with clonazepam or alprazolam within 2 weeks of the trauma (Gelpin et al. 1996); no difference was observed at 1–6 months between these patients and a control group.

A novel approach has attempted very early secondary prevention within hours (or days) of the traumatic event by reducing noradrenergic activation. This approach builds on the proposal that blocking noradrenergically based consolidation of the trauma memories in the acute phase will limit the extent of fear conditioning and thereby result in less PTSD (Cahill et al. 1994). An initial pilot study found that propranolol was associated with lower reactivity to trauma reminders 3 months after the trauma compared with a placebo condition; however, it did not result in reduced PTSD (Pitman et al. 2002). An uncontrolled study found that administration of propranolol immediately following a traumatic event was related to reduced PTSD after 2 months (Vaiva et al. 2003). In an attempt to replicate these studies, Stein and colleagues administered propranolol to trauma survivors within 48 hours of exposure but did not find that it resulted in reduced PTSD relative to placebo (Stein et al. 2007). Consistent with this, a review of medical records indicated that propranolol administered in the first 30 days following burn trauma did not reduce ASD symptoms in children who had experienced burn trauma (Sharp et al. 2010). Another recent study suggests that there may be differential gender effects for the impact of propranolol on traumatic stress symptoms in children (Nugent et al. 2010).

Another line of inquiry has addressed the role of glucocorticoids in the initial phase after trauma exposure. There is some evidence that patients in medical settings who were administered cortisol developed fewer traumatic memories than those who were not (Schelling et al. 2001, 2004a). This finding accords with evidence that animals administered hydrocortisone immediately after a stressor displayed less anxiety than those administered a placebo (Cohen et al. 2008). This raises the possibility that secondary prevention of PTSD may be achieved by cortisol administration (Schelling et al. 2004b). One randomized controlled trial administered high-dose hydrocortisone within hours of trauma exposure and found that it led to less ASD, as well as later PTSD, than placebo (Zohar et al. 2011). Although preliminary, these data point to the potential for secondary prevention through direct modulation of glucocorticoid release in the acute phase.

There is also preliminary evidence that administration of morphine in the immediate hours after trauma is associated with reduced PTSD symptoms assessed at a later date (Bryant et al. 2009; Holbrook et al. 2010; Saxe et al. 2001). These findings accord with evidence that morphine injections into the amygdala of rats impair acquisition of fear conditioning (Clark et al 1972) and also cause amnesia for fear conditioning in rats (McNally and Westbrook 2003). Despite this promising association, these studies were naturalistic studies rather than randomized controlled trials and therefore do not provide strong evidence.

Implications of the DSM-5 Diagnosis

All treatment studies to date have been based on DSM-IV criteria for ASD or acute PTSD. Changes to the DSM-5 criteria have several implications for interpreting the current studies on treating ASD (see Box 28–1). First, in terms of the stated goal of the ASD diagnosis in DSM-5, it no longer attempts to predict who will develop subsequent PTSD because the available evidence points to a limited utility of the diagnosis in achieving adequate prediction (Bryant et al. 2011). Accordingly, the clinical goal of the ASD diagnosis in DSM-5 is to identify people who are severely distressed in the initial month so their current clinical needs can be addressed. This places greater emphasis on treating acute stress reactions rather than preventing subsequent PTSD. Second, the DSM-5 criteria no longer require that specific clusters be satisfied but rather that the person simply displays at least 9 of a potential 14 symptoms in the initial month after trauma exposure. This new definition results in the ASD criteria presenting more as severe acute PTSD (or rather acute subsyndromal PTSD because it does not require that all clusters be satisfied), and in this sense it highlights the relevance of available studies that have focused on acute PTSD. Third, and most importantly, the available studies of treating ASD remain highly relevant to the DSM-5 definition of ASD. Although there is no longer the requirement that clusters be satisfied, the requirement of 9 symptoms necessitates that some form of reexperiencing or avoidance symptoms are present. This underscores the utility of exposure-based treatment, which forms the basis of most supported psychotherapy trials to date.

Box 28–1. DSM-5 Diagnostic Criteria for Acute Stress Disorder

308.3 (F43.0)

A. Exposure to actual or threatened death, serious injury, or sexual violation in one (or more) of the following ways:

1. Directly experiencing the traumatic event(s).
2. Witnessing, in person, the event(s) as it occurred to others.
3. Learning that the event(s) occurred to a close family member or close friend. **Note:** In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains, police officers repeatedly exposed to details of child abuse).

Note: This does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

B. Presence of nine (or more) of the following symptoms from any of the five categories of intrusion, negative mood, dissociation, avoidance, and arousal, beginning or worsening after the traumatic event(s) occurred:

Intrusion Symptoms

1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). Note: In children, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.
2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the event(s). **Note:** In children, there may be frightening dreams without recognizable content.
3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) **Note:** In children, trauma-specific reenactment may occur in play.
4. Intense or prolonged psychological distress or marked physiological reactions in response to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

Negative Mood

5. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

Dissociative Symptoms

6. An altered sense of the reality of one's surroundings or oneself (e.g., seeing oneself from another's perspective, being in a daze, time slowing).
7. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).

Avoidance Symptoms

8. Efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
9. Efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

Arousal Symptoms

10. Sleep disturbance (e.g., difficulty falling or staying asleep, restless sleep).
11. Irritable behavior and angry outbursts (with little or no provocation), typically expressed as verbal or physical aggression toward people or objects.
12. Hypervigilance.
13. Problems with concentration.
14. Exaggerated startle response.

C. Duration of the disturbance (symptoms in Criterion B) is 3 days to 1 month after trauma exposure.

Note: Symptoms typically begin immediately after the trauma, but persistence for at least 3 days and up to a month is needed to meet disorder criteria.

D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E. The disturbance is not attributable to the physiological effects of a substance (e.g., medication or alcohol) or another medical condition (e.g., mild traumatic brain injury) and is not better explained by brief psychotic disorder.

Challenges for Treating ASD

Whether one is using pharmacological or psychotherapeutic approaches to managing ASD, there are several key challenges facing clinicians. In the acute phase after trauma, it is often very difficult to facilitate help seeking in those who most require interventions because of the competing medical, social, or other demands that are placed on the trauma survivor. Numerous studies have highlighted the reluctance of recently traumatized people to seek mental health treatment (Brewin et al. 2008; Stuber et al. 2006; Weisaeth 2001). Worryingly, there is evidence that nonacceptance of treatment that is offered is associated with less improvement at subsequent follow-up (Shalev et al. 2011).

Another challenge is the issue of treating potential transient stress responses, and in this sense treating unnecessarily. A significant proportion of people who meet the criteria for ASD do not develop longer-term PTSD, yet we do not have reliable means to discern between those who are experiencing a transient stress response and those who are not. Especially in large-scale traumatic events, such as natural disasters, there is a need to allocate limited mental health resources to those who are most in need. Although DSM-5 has explicitly recognized that the goal of ASD is not to predict subsequent reactions, there is also the need to minimize the possibility of treating people who will recover without intervention. This issue is compounded by increasing evidence that the course of PTSD is not consistent over time but rather that people have fluctuating courses of PTSD that can involve different trajectories (Bonanno et al. 2012, 2013; Bryant et al. 2013). This pattern underscores the difficulty we face in trying to identify shortly after a traumatic event people who are going to experience longer-term difficulties. Despite this difficulty, one needs to balance meeting the apparent clinical needs in the aftermath of trauma with resources that are available, and at this point in time the ASD diagnosis appears to be a reasonable means to target treatment to those in most need.

Conclusion

Since the introduction of the ASD diagnosis in 1994, we have learned a great deal about the nature of acute stress responses and both how we may ameliorate them in the short term and how short-term amelioration can lead to longer-term benefits. Although pharmacological agents are showing promising signs for secondary prevention, the strength of evidence for trauma-focused psychotherapy approaches strongly indicates that this method is the treatment of choice for ASD. Although less intense and labor intensive than CBT for chronic PTSD, these interventions still require multiple sessions of therapy and require highly qualified clinicians. In this sense, this treatment is resource demanding, and this raises challenges for the capacity to implement CBT treatments in posttrauma

settings where demand outstrips supply of appropriate mental health services. This highlights that research needs to develop and evaluate modifications of current CBT treatments so they can be more readily accessible to people who can benefit from them in the acute phase.

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CHAPTER 29

Adjustment Disorders

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Adjustment disorders (ADs) occupy a special place in the taxonomy of psychiatry—the *Diagnostic and Statistical Manual of Mental Disorders*—between normal problems of living and threshold diagnoses: that is, they have been until now regarded as subthreshold diagnoses (American Psychiatric Association 1994, 2013). Most medical diseases and psychiatric illnesses have symptom or laboratory checklists or findings to aid and objectify the diagnosis, which is essential for the appropriate application of treatment.

AD is a stress-induced diagnosis, and the patient's functionality and distress are affected. However, ADs do not have a symptom checklist or a symptom profile calibrated to obtain an *objective* assessment of dysfunction or distress.

The very nonspecificity of the AD diagnosis provides great clinical utility because it provides a placement for significant clinical states that do not conform to another DSM-5 diagnosis but are of sufficient severity to qualify as a psychiatric disorder, whether as end-stage diagnostic entities in their own right or as prodromal expressions of more discrete disorders yet to emerge (Bryant et al. 2011; Friedman et al. 2011; Strain and Friedman 2011). There is no agreed-on standardized diagnostic instrument for epidemiological research or clinical trials for ADs (Strain and Friedman 2011). At present the "gold standard" for diagnosing ADs remains the trained clinician—with understandably a significant degree of subjectivity involved.

For both DSM-5 and ICD-11 it has been decided that the ADs are classified within a new genre, *trauma- and stressor-related disorders,* alongside PTSD and ASD (Friedman et al. 2011). This classification invites the examination of ADs with respect to psychobiological mechanisms, for example, altered hypothalamic-pituitary-adrenocortical (HPA) function, and provides a useful heuristic that may encourage both basic research and clinical trials (Strain and Friedman 2011); enhances understanding of the relationships between stress response syndromes, depression,

anxiety disorders, and PTSD (Friedman et al. 2011; Strain and Friedman 2011); and advances the understanding of how the HPA and related systems operate in ADs and whether each AD subtype exhibits similar psychobiological alterations. Given the research demonstrating stress-related HPA reactions (Bryant et al. 2011; Friedman et al. 2011; Strain and Friedman 2011), it is useful to determine how different AD subtypes are associated with HPA function and how HPA function among AD subtypes compares with HPA activity observed in parent disorders such as major depression.

An important aspect of treatment of the stress-related disorders has been the consideration of resilience; what are its progenitors and how can it be fostered so that the severity and/or endurance of an adverse reaction to a traumatic stressor may be mitigated (Charney 2004; Southwick and Charney 2012)? Resilience offers a third approach to the treatment of the stress-related disorders, including the ADs: psychotherapy, psychopharmacology, and resilience.

Psychotherapy

Treatment of ADs relies primarily on psychotherapeutic measures that enable reduction of the stressor, enhanced coping with stressors that cannot be reduced or removed, and establishment of a support system to maximize adaptation.

The first goal is to note significant dysfunction secondary to a stressor and to help the patient moderate this imbalance. Many stressors (e.g., taking on more responsibility than can be managed by the individual or putting oneself at risk by having unprotected sex with an unknown partner) may be avoided or minimized. Other stressors (e.g., abandonment by a lover) may elicit an overreaction. The patient may attempt suicide or become reclusive or damage his or her source of income. The therapist assists the patient with minimizing distress and other feelings by putting them into words rather than into destructive actions; more optimal adaptation and mastery of the trauma or stressor are sought.

The role of verbalization cannot be overestimated as an effective approach for reducing the impact of the stressor and to enhance coping. The therapist needs to clarify and interpret the meaning of the stressor for the patient. For example, a mastectomy may have devastated a patient's feelings about her body and herself. It is necessary to clarify that the patient is still a woman, capable of having a fulfilling relationship, including a sexual one, and that the patient can have the cancer removed or treated and not necessarily have a recurrence. Otherwise, the patient's pernicious fantasies—"all is lost"—may take over in response to the stressor (i.e., the mastectomy) and make her dysfunctional in work and/or sex and in relationships and may precipitate a painful disturbance of mood that is incapacitating.

Counseling, Cognitive-Behavioral Therapy, Crisis Intervention, Supportive Group Treatment, and Family Therapy

Counseling (including medical crisis counseling), cognitive-behavioral therapy (CBT), crisis intervention, supportive group treatment, and family therapy may be employed to encourage the verbalization of fears, anxiety, rage, helplessness, and hopelessness related to the stressors imposed (or self-imposed) on a patient.

The goals of treatment in each case are to expose the concerns and conflicts that the patient is experiencing, to identify strategies to reduce the stressors, to enhance the patient's coping skills, to help the patient gain perspective on the adversity, and to establish relationships (e.g., a support network) to assist in the management of the stressors and the self. CBT has been successfully used in young military recruits (Nardi et al. 1994).

Brief Psychotherapy

In terms of the DSM-III-R criteria (American Psychiatric Association 1987), Sifneos (1989) stated that patients with ADs profit most from brief psychotherapy. The psychotherapy should attempt to reframe the meaning of the stressor(s). Although brief therapeutic interventions are often sufficient, ongoing stressors or enduring character pathology that may make a patient vulnerable to stress intolerance may signal the need for lengthier treatments.

Many types of therapeutic modalities have a place in the treatment of ADs. Wise (1988), drawing from military psychiatry, emphasized the treatment variables of brevity, immediacy, centrality, expectance, proximity, and simplicity (BICEPS principles). The treatment approach is brief—usually no more than 72 hours and focuses on the immediate stressors (True and Benway 1992).

Interpersonal Psychotherapy

Interpersonal psychotherapy (IPT) was applied to depressed HIV-positive outpatients and found to be effective (Markowitz et al. 1992). The mechanisms of IPT are important in understanding psychotherapeutic approaches to the ADs: 1) psychoeducation about the sick role, 2) a here-and-now framework, 3) formulation of the problems from an interpersonal perspective, 4) exploration of options for changing dysfunctional behavior patterns, 5) identification of focused interpersonal problem areas, and 6) the confidence that therapists gain from a systematic approach to problem formulation and treatment.

Interventions for Elderly Patients

Elderly patients are particularly vulnerable to the development of ADs as the stress of interpersonal losses, medical illness, and multiple medications abound. Life transitions such as relocating to a nursing home or losing one's driving privileges are commonly experienced as stressors in the elderly. A treatment that strengthens a patient's ego functions by helping the patient acknowledge the stressor and by promoting effective coping strategies is useful in this population. An active therapeutic stance and the use of life review foster a sense of mastery over the stressor.

Support Groups

Support groups are employed in patients with ADs to adjust and enhance their coping mechanisms (Fawzy et al. 2003; Spiegel et al. 1989). Studies of the survival benefits of psychosocial group interventions have yielded mixed results. Cancer patients who attended support groups have shown increased survival time, improvements in mood, reduced distress level, and enhanced quality of life (Akechi et al. 2008; Goodwin et al. 2001; Newell et al. 2002; Spiegel 2011; Spiegel et al. 2007). More research is needed to determine whether other stress-related disorders are improved by such systematic and carefully defined behavioral interventions.

Eye Movement Desensitization and Reprocessing

Eye movement desensitization and reprocessing (EMDR) has been studied in patients with ADs. EMDR, which is effective in the treatment of PTSD, was used in treating nine patients with ADs (Mihelich 2000). Significant improvement in anxiety or mixed features was seen, but not among patients with depressed mood; those patients with ongoing stressors did not demonstrate improvement. There is no evidence that the eye movement component of the therapy (vs. attention, talking, showing interest) adds to its benefit.

Akechi et al. (2004) investigated associated and predictive factors in cancer patients with AD and major depression. Findings revealed that psychological distress in these patients was associated with a variety of factors, including reduced social support, impaired physical functioning, and existential concerns. This highlights the necessity of a multidimensional care plan for the treatment of ADs that includes physical, psychosocial, and existential components. Studies have yet to evaluate the potential role of family and couples therapy as well as treatments from complementary and alternative medicine such as acupuncture and yoga.

Mirror Therapy

As of this writing, the Cochrane Database of Systematic Reviews contains only two randomized controlled trials (RCTs) of specific psychotherapeutic treatment of ADs. González-Jaimes and Turnbull-Plaza (2003) observed that "mirror psychotherapy" for AD patients with depressed mood secondary to a myocardial infarction was both an efficient and an effective treatment. Mirror therapy is described as comprising psychocorporal, cognitive, and neurolinguistic components with a holistic focus. As part of the treatment, a mirror is used to encourage the patient to accept his or her physical limitations that resulted from the lack of past self-care behaviors. In González-Jaimes and Turnbull-Plaza's study, mirror therapy was compared with a control condition and two other treatments: Gestalt psychotherapy and medical conversation. Depressive symptoms improved in all treatment groups compared with the control sample, but mirror therapy was significantly more effective than the other treatments in decreasing symptoms of an AD at posttest evaluation.

Occupational Intervention and Cognitive-Behavioral and Problem-Solving Treatment

In another RCT, an "activating intervention" for ADs was employed for occupational dysfunction (van der Klink and van Dijk 2003; van der Klink et al. 2003). In this study, 192 employees were randomly assigned to receive either the intervention or usual care. The intervention consisted of an individual cognitive-behavioral approach to a graded activity, similar to stress inoculation training. Workers were asked to do more demanding and complicated activities as treatment progressed. Goals of treatment emphasized the acquisition of coping skills and the regaining of control. The treatment proved to be effective in decreasing sick leave duration and shortening long-term absenteeism when compared with the control cohort. Both intervention and control groups, however, showed similar amounts of symptom reduction. This study formed the basis for the "Dutch Practice Guidelines for the Treatment of

ADs in Primary and Occupational Health Care" (van der Klink and van Dijk 2003), which were prepared by 21 occupational health physicians and 1 psychologist and were subsequently reviewed and tested by 15 experts, including several psychiatrists and psychologists.

Nine other RCTs with interventions involving the workplace have been accomplished using CBT and problem-solving treatment. Of the 59 published studies, only 9 were considered scientifically adequate to be included in the Cochrane Database meta-analysis. Even the 9 studies selected had the major problem of heterogeneity of psychiatric diagnosis. "Burn out," "stress," "neurasthenia," "work-related stress," and "minor mental disorder" were considered as diagnoses of AD in several studies, which further dilutes the definition of this already problematically defined psychiatric disorder. Some studies were included if as few as 30% of the diagnoses were "pure" AD. Finally, AD was diagnosed using varied criteria, screening instruments, and diagnosticians.

Brief Dynamic Therapy and Brief Supportive Therapy

Although no other RCTs involving the psychotherapeutic treatment of pure cohorts of patients with ADs could be found, many RCTs exist that focused on an array of depressive and anxiety disorders and included ADs in their cohorts. A trial comparing brief dynamic therapy with brief supportive therapy in patients with minor depressive disorders, including ADs (therefore a mixed diagnostic sample), was reported in the Cochrane Database. Although both therapies proved efficacious in reducing symptoms, brief dynamic therapy was more effective than brief supportive therapy at 6-month follow-up (Maina et al. 2005).

Pharmacotherapy

Although psychotherapy is the mainstay of treatment for ADs, psychopharmacological intervention can be especially helpful in the treatment of minor depression (Stewart et al. 1992; Strain et al. 1998). There is a significant difference between minor depression and AD with depressed mood. Minor depression requires dysphoria and/or anhedonia plus two other ideational or vegetative symptoms (e.g., lack of energy and suicidality). The symptoms can be from any of the eight systems listed for major depressive disorder in DSM-5. Stewart et al. (1992) argued that pharmacotherapy is generally recommended, but data do not support this contention. Despite the lack of rigorous scientific evidence, Stewart and colleagues advocated successive trials with antidepressants for any depressed patient (major or minor disorders), particularly if he or she has not benefited from psychotherapy or other supportive measures after 3 months. The authors do not mention AD with depressed mood in particular. In an RCT in the treatment of minor depressive disorder, fluoxetine proved superior to placebo in reducing depressive symptoms, improving overall psychosocial functioning, and alleviating suffering (Judd 2000). The question remains, does this also apply to ADs with depressed mood?

RCTs of pharmacotherapy in patients with ADs are rare. Formal psychotherapy appears to be the current treatment of choice (Uhlenhuth et al. 1995), although psychotherapy combined with benzodiazepines also is used, especially for patients with a severe life stressor(s) and a significant anxiety component (Shaner 2000; Uhlenhuth et al. 1995). Tricyclic antidepressants or buspirone have been recommended in place of benzodiazepines

for patients with current or past heavy alcohol use because of the greater risk of dependence (Uhlenhuth et al. 1995). In a 25-week multicenter RCT, WS 1490 (a special extract from kava kava) was reported to be effective in AD with anxiety compared with placebo and did not produce side effects, as is the case with tricyclic antidepressants and benzodiazepines (Volz and Kieser 1997).

In another RCT, Bourin et al.(1997) assigned patients to receive either Euphytose—a preparation containing a combination of plant extracts (*Crataegus, Ballota, Passiflora,* and *Valeriana,* which have mild sedative effects, and *Cola* and *Paullinia,* which mainly act as mild stimulants) or placebo. Patients taking the experimental drugs improved significantly more than those taking placebo. In another study, tianeptine, alprazolam, and mianserin were found to be equally effective in symptom improvement in patients with AD with anxiety (Ansseau et al. 1996). In another RCT, trazodone was more effective than clorazepate in cancer patients for the relief of anxiety and depression symptoms (Razavi et al. 1999). Similar findings were observed in HIV-positive patients with ADs (DeWit et al. 1999).

There are no RCTs employing selective serotonin reuptake inhibitors, other antidepressants, or anxiolytics (e.g., nefazodone, venlafaxine, buspirone, or mirtazapine). These medications may offer symptom relief of dysphoric or anxious moods. The difficulty in obtaining an AD study cohort with reliable and valid diagnoses may impede the carrying out of an RCT comparing these agents with both placebo and psychotherapy.

Clinical trials regarding ADs are also compromised by not having specific symptoms to monitor when the outcome of an intervention is being examined. In the case of the ADs, should the assessment take place when the stressors have stabilized, when the stressors have abated, or after an agreed-on time (e.g., 3 months) has elapsed? The stressor attributes add a further confound to obtaining a homogeneous sample because of the differences in the stressors, including their nature (quality), severity (quantity), and acuteness (less than 6 months) or chronicity (more than 6 months).

Psychotropic medication was used with medically ill patients, terminally ill patients, and patients with illness refractory to verbal therapies. Many of these patients had an AD, but it cannot be ascertained if some had minor depression. In a study of medically ill patients with depressive disorders (it is unspecified which depressive disorders were studied, and the disorders may not have been ADs), Rosenberg et al. (1991) reported that 16 of 29 patients (55%) improved within 2 days of treatment with the maximal dosage of amphetamine derivatives. The presence of delirium was associated with a decreased response. Whether methylphenidate would be useful in ADs with depressed mood remains to be investigated, but this medication has the problem of potential for addiction.

In a review of RCTs, Reynolds (1992) stated that bereavement-related syndromal depression also appears to respond to antidepressant medication. If medication is prescribed for minor disorders (including subthreshold disorders), the predominant mood that accompanies the (adjustment) disorder is an important consideration. Schatzberg (1990) recommended that therapists consider both psychotherapy and pharmacotherapy in ADs with anxious mood and that anxiolytics should be part of psychiatrists' armamentarium. Using an RCT, Nguyen et al. (2006) compared the efficacies of etifoxine, a nonbenzodiazepine anxiolytic drug, and lorazepam, a benzodiazepine, in the treatment of AD with anxiety in a

primary care setting. Efficacy was evaluated on days 7 and 28 using the Hamilton Rating Scale for Anxiety. The two drugs were found to be equivalent in anxiolytic efficacy on day 28. However, more etifoxine recipients than lorazepam recipients responded to the treatment. One week after stopping treatment, fewer patients taking etifoxine experienced rebound anxiety compared with those stopping lorazepam.

A new Cochrane Database meta-analysis is under way examining the psychopharmacological treatment of ADs. This is an important investigation because few RCTs of psychopharmacological treatment for ADs exist. However, as with the Cochrane Database meta-analysis of RCTs in the workplace, there are many concerns about the diagnostic integrity of the patient cohorts being examined. In this proposed review the researchers state that the terms "situational disturbance," "reactive," "mild, minor, situational," "subthreshold subsyndromal," and "subclinical depression" will be used interchangeably with the diagnosis of AD. This heterogeneity of diagnosis would keep the Cochrane Database meta-analyses from being the gold standard for producing data that enhance validated evidence-based interventions.

Understanding the etiology of depression and its treatment has advanced with the discoveries of neurobiology of affective disorders and the utilization of animal models. The neurobiology of major disorders, including the anxiety disorders, may offer new pathways for the minor, subsyndromal diagnoses as well. Duman and Aghjanian (2012) have presented their perspective on synaptic dysfunction in depression and potential therapeutic targets. Ketamine, an *N*-methyl-D-aspartate receptor antagonist, produces rapid antidepressant responses, induces synaptogenesis, and reverses the synaptic deficits caused by chronic stress. This would include neuronal atrophy and decreases in synaptic density (synaptic loss). Would this mechanism of therapeutic action have any effect on AD with depressed mood, especially the chronic form? Is neurogenesis a pathway to recovery from a mood disorder? As Duman and Aghajanian (2012) note, the neurogenic hypothesis of mood disorders may be an important building block for understanding the causes of depression and offer new approaches to treatment. This emphasizes the need to know the relationship, if any, between subsyndromal symptoms and fully developed symptom profiles of the major syndromes. This would enhance our understanding of the treatment regimens that may be utilized with ADs.

Regardless of whether psychotherapy and pharmacotherapy are used alone or in combination, a significant aspect of treatment is to recognize that the diagnosis of AD may indicate a patient who is in the early phase of a major mental disorder that has not yet evolved to full-blown symptoms. If a patient continues to worsen, becomes more symptomatic, and does not respond to treatment, it is critical to review the patient's symptom profile and consider whether the AD has progressed to a major mental disorder. The patient undergoing a mastectomy in the case example discussed earlier may have been in the early phase of a major depressive disorder, but at the time of assessment, her clinical presentation met criteria only for AD with depressed mood, a subthreshold mood disorder.

Resilience

Southwick and Charney (2012) have emphasized the need to better understand the psychobiology of resilience as an im-

portant component of effective treatment for stress-induced dysfunction and distress. They emphasize that persons react remarkably differently to stress: how individuals respond to stress depends on numerous genetic, developmental, cognitive, psychological, and neurobiological risk and protective factors. Southwick and Charney (2012) state that "resilience is generally understood as the ability to bounce back from hardship and trauma" (p. 79). The American Psychological Association defines resilience as "the process of adapting well in the face of adversity, trauma, tragedy, threats or even significant sources of threat" (Southwick and Charney 2012, p. 79). Overwhelming stressors in childhood may lead to "giving in and giving up" when confronted by stressors later in life, whereas manageable stressors in childhood may actually strengthen the individual's capacity to cope with subsequent stress. Southwick and Charney (2012) have schematized stressors and genetic predisposition (Table 29–1). This conceptual framework is an entirely different way of systematizing the etiology of distress and dysfunction in ADs and also offers an alternative route to treatment. The authors adumbrate neurobiological interventions: developing therapeutic agents to contain stress-induced overdrive of corticotropin-releasing hormone, which controls and integrates the body's response to stress, would likely reduce rates of trauma-related (stress-related) psychopathology.

Charney (2004) has outlined the critical elements of human resilience:

- Faith or spirituality
- Humor
- Role models
- Social supports
- Facing fear, being out of one's comfort zone, challenges
- A life's mission
- Training (in all its forms)
- Character strengths and virtues; altruism and optimism
- Moral compass or a code of honor

Southwick and Charney (2012) offer a prescription for resilience:

1. Have a positive attitude.
2. Utilize cognitive flexibility through cognitive reappraisal.
3. Embrace a personal moral compass.
4. Find a resilient role model.
5. Face your fears; accept challenges.
6. Develop active coping skills.
7. Establish and nurture a supportive social network.
8. Attend to physical well-being.
9. Train regularly and rigorously in multiple areas.
10. Recognize, utilize, and foster signature strengths.

A different conceptual framework for treatment of a stress-related event (not psychotherapy or psychopharmacology) might also include interventions to strengthen resilience beforehand, thereby equipping individuals to cope more effectively with any future stressors. Further studies of the ingredients of resilience may help shape the "development of evidence-based interventions to mitigate risk for depression and to enhance resilience to stress" (Southwick and Charney 2012, p. 82). Obviously, enhanced resilience would also mitigate the risk for anxiety disorders, posttraumatic stress disorder, adjustment disorders, among other disorders.

Conclusion

Adjustment disorders are the most common diagnoses in the military, in children, and in psychosomatic medicine and

TABLE 29–1. Components underlying resilience

	Environmental stressors and genetic predisposition		
	Depression risk factors	**Therapeutic intervention**	**Resilience protective factors**
Cognitive-behavioral	Weak executive function: weak coping self-efficiency; negative attention bias; cognitive inflexibility	Cognitive-behavioral therapy with cognitive reappraisal; positive emotion exercises, coping skill development, and training; well-being therapy	Strong executive function; high coping self-efficacy; positive emotions; realistic optimism; cognitive flexibility
Emotion regulation	Weak regulation (e.g., anhedonia; slow stress recovery)	Mindfulness; training; antidepressant medications	Strong regulation (e.g., delay gratification; rapid stress recovery)
Social	Weak social skills; minimal social network; no resilient role models	Social emotional training; network support treatment	Strong social skills; diverse social network; resilient role models
Physical health	Sleep deprivation; poor cardiovascular fitness; poor nutrition; obesity	Teach sleep hygiene; exercise regimen; improve diet	Strong sleep habits; physically fit; good nutrition
Neurobiology	Dysregulated HPA axis and SNS in response to stress; attenuated prefrontal cortical executive function and stress-induced limbic system hyperactivity	Neural circuit training; novel medications (corticotropin-releasing factor, neuropeptide Y, GABA, glutamate)	Effective regulation of HPA axis and SNS in response to stress; robust prefrontal cortical executive function and capacity to regulate limbic reactivity to stress

Note. GABA=γ-aminobutyric acid; HPA=hypothalamic-pituitary-adrenal; SNS=sympathetic nervous system.

Source. Reprinted from [illegible] Depression." *Science*

consultation-liaison psychiatry, yet little is known because these diagnoses have questionable reliability and validity. No specific screening instrument can authenticate the presence of an AD, and there are few outcome studies from the current interventions. How many individuals with AD have spontaneous recovery, how many go on to major disorder symptomatology, and how many retain a chronic form of the subsyndromal AD? It is essential to learn more not only about diagnosing this most common mental disorder but also about the interventions most likely to have a salutatory response and in what setting (e.g., integrated primary care health settings). With the excitement of current and future neuroscience breakthroughs, we are poised to gain a more rigorous understanding of these ubiquitous disorders.

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PART VI

Somatic Symptom and Related Disorders and Eating Disorders

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Somatic Symptom and Related Disorders

In DSM-5, somatoform disorders have been renamed and are now referred to as "somatic symptom and related disorders." To facilitate differential diagnosis, the authors of DSM-5 moved factitious disorder and psychological factors affecting another medical condition into this diagnostic class. Body dysmorphic disorder, however, is now included with the obsessive-compulsive and related disorders.

Because many of the somatoform disorders overlapped, the authors of DSM-5 decided to regroup these disorders as shown in Figure 1. Hypochondriasis has been split into two disorders. In a minority of cases, there are prominent health concerns but few actual somatic symptoms. This presentation is now termed *illness anxiety disorder* (see Box 1). In the rest of hypochondriasis, there are disproportionate health concerns associated with somatic symptoms, and this is recognized as a variant of somatic symptom disorder. Somatic symptom disorder also encompasses DSM-IV somatization disorder and undifferentiated somatoform disorder, as well as the pain disorders.

Box 1. DSM-5 Diagnostic Criteria for Illness Anxiety Disorder

300.7 (F45.21)

A. Preoccupation with having or acquiring a serious illness.
B. Somatic symptoms are not present or, if present, are only mild in intensity. If another medical condition is present or there is a high risk for developing a medical condition

(e.g., strong family history is present), the preoccupation is clearly excessive or disproportionate.

C. There is a high level of anxiety about health, and the individual is easily alarmed about personal health status.

D. The individual performs excessive health-related behaviors (e.g., repeatedly checks his or her body for signs of illness) or exhibits maladaptive avoidance (e.g., avoids doctor appointments and hospitals).

E. Illness preoccupation has been present for at least 6 months, but the specific illness that is feared may change over that period of time.

F. The illness-related preoccupation is not better explained by another mental disorder, such as somatic symptom disorder, panic disorder, generalized anxiety disorder, body dysmorphic disorder, obsessive-compulsive disorder, or delusional disorder, somatic type.

Specify whether:

Care-seeking type: Medical care, including physician visits or undergoing tests and procedures, is frequently used.

Care-avoidant type: Medical care is rarely used.

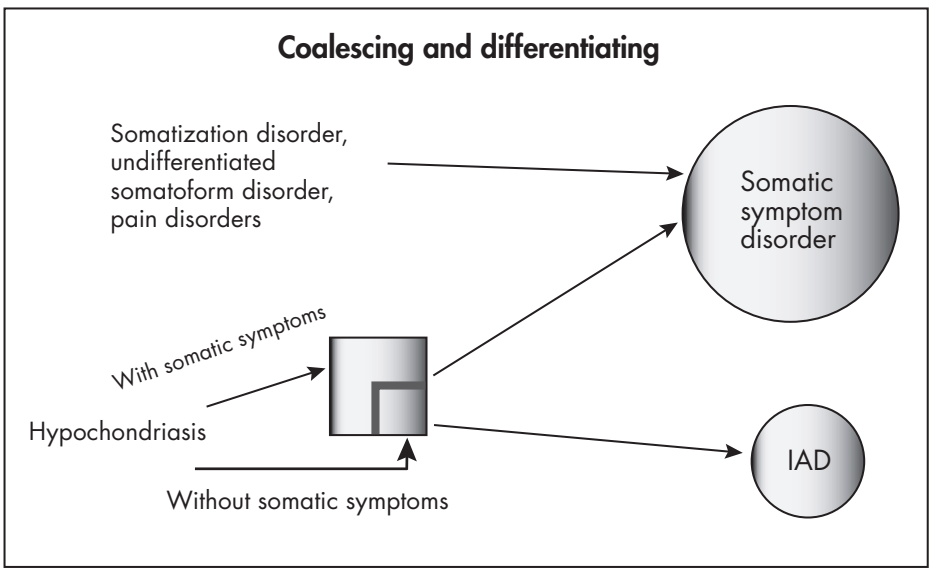

FIGURE 1. Changes in somatic symptom disorders from DSM-IV to DSM-5.

Somatic symptom disorder (see Box 2) is characterized by prominent and persistent (>6 months) somatic complaints associated with disproportionate and excessive thoughts, feelings, and behaviors related to these complaints. Note that medically unexplained symptoms are not a key feature in this disorder. Rather, the guidelines recognize that these disorders sometimes occur with or without a medical explanation. All suffering is legitimate, regardless of the medical explanation.

Box 2. DSM-5 Diagnostic Criteria for Somatic Symptom Disorder

300.82 (F45.1)

A. One or more somatic symptoms that are distressing or result in significant disruption of daily life.
B. Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following:
   1. Disproportionate and persistent thoughts about the seriousness of one's symptoms.
   2. Persistently high level of anxiety about health or symptoms.
   3. Excessive time and energy devoted to these symptoms or health concerns.
C. Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically more than 6 months).

Specify if:

With predominant pain (previously pain disorder): This specifier is for individuals whose somatic symptoms predominantly involve pain.

Specify if:

Persistent: A persistent course is characterized by severe symptoms, marked impairment, and long duration (more than 6 months).

Specify current severity:

Mild: Only one of the symptoms specified in Criterion B is fulfilled.
Moderate: Two or more of the symptoms specified in Criterion B are fulfilled.
Severe: Two or more of the symptoms specified in Criterion B are fulfilled, plus there are multiple somatic complaints (or one very severe somatic symptom).

Conversion disorder (functional neurological symptom disorder) (see Box 3) has been modified for DSM-5 primarily by the clarification that the symptoms are not just medically *unexplained* but medically *inconsistent*. Psychological factor affecting medical condition, included in "Other Conditions That May Be a Focus of Clinical Attention" in DSM-IV, has been moved to the somatic symptom and related disorders, and the subtypes have been dropped. In factitious disorders, DSM-IV distinguished between factitious psychological presentations and medical presentations; that distinction has been dropped in DSM-5.

Box 3. DSM-5 Diagnostic Criteria for Conversion Disorder (Functional Neurological Symptom Disorder)

A. One or more symptoms of altered voluntary motor or sensory function.
B. Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions.
C. The symptom or deficit is not better explained by another medical or mental disorder.
D. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

Coding note: The ICD-9-CM code for conversion disorder is **300.11,** which is assigned regardless of the symptom type. The ICD-10-CM code depends on the symptom type (see below).

Specify symptom type:

(F44.4) With weakness or paralysis

(F44.4) With abnormal movement (e.g., tremor, dystonic movement, myoclonus, gait disorder)

(F44.4) With swallowing symptoms

(F44.4) With speech symptom (e.g., dysphonia, slurred speech)

(F44.5) With attacks or seizures

(F44.6) With anesthesia or sensory loss

(F44.6) With special sensory symptom (e.g., visual, olfactory, or hearing disturbance)

(F44.7) With mixed symptoms

Specify if:

Acute episode: Symptoms present for less than 6 months.

Persistent: Symptoms occurring for 6 months or more.

Specify if:

With psychological stressor *(specify stressor)*

Without psychological stressor

Eating Disorders

Many of the changes to the diagnostic criteria for the eating disorders from DSM-IV to DSM-5 were aimed at reducing the prevalence of the eating disorder not otherwise specified (EDNOS) category. Most significant of these changes is the inclusion of one of the few new diagnostic entities approved for DSM-5, *binge-eating disorder,* or BED (see Box 4). In DSM-IV, individuals with BED were diagnosed as having EDNOS. In DSM-5, BED is characterized by binge eating at a regular frequency (at least one episode per week for 3 months) without compensatory behavior, which is what distinguishes it from bulimia nervosa (BN), in which there is binge eating with compensation. As a result of the lack of compensatory behaviors, many patients with BED are obese, another feature that distinguishes BED individuals from those with BN, who are typically at a normal weight.

Box 4. DSM-5 Diagnostic Criteria for Binge-Eating Disorder

307.51 (F50.8)

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:

1. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than what most people would eat in a similar period of time under similar circumstances.
2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).

B. The binge-eating episodes are associated with three (or more) of the following:

1. Eating much more rapidly than normal.
2. Eating until feeling uncomfortably full.
3. Eating large amounts of food when not feeling physically hungry.

4. Eating alone because of feeling embarrassed by how much one is eating.
5. Feeling disgusted with oneself, depressed, or very guilty afterward.

C. Marked distress regarding binge eating is present.

D. The binge eating occurs, on average, at least once a week for 3 months.

E. The binge eating is not associated with the recurrent use of inappropriate compensatory behavior as in bulimia nervosa and does not occur exclusively during the course of bulimia nervosa or anorexia nervosa.

Specify if:

In partial remission: After full criteria for binge-eating disorder were previously met, binge eating occurs at an average frequency of less than one episode per week for a sustained period of time.

In full remission: After full criteria for binge-eating disorder were previously met, none of the criteria have been met for a sustained period of time.

Specify current severity:

The minimum level of severity is based on the frequency of episodes of binge eating (see below). The level of severity may be increased to reflect other symptoms and the degree of functional disability.

Mild: 1–3 binge-eating episodes per week.

Moderate: 4–7 binge-eating episodes per week.

Severe: 8–13 binge-eating episodes per week.

Extreme: 14 or more binge-eating episodes per week.

There are significant changes to the diagnostic criteria for anorexia nervosa (AN) (see Box 5). Criterion A from DSM-IV ("Refusal to maintain body weight at or above a minimally normal weight for age and height") has been removed. This change was made to address the implication that individuals with AN volitionally choose to lower their body weight and can if they choose easily reverse this pattern and gain weight. Criterion A now simply states that the disorder is characterized by caloric restriction leading to "significantly low body weight in the context of age, sex, developmental trajectory, and physical health," without quantifying how much weight loss is required. In addition, in Criterion B, the phrase "Intense fear of gaining weight or becoming fat" has been changed to include the phrase "or persistent behavior that interferes with weight gain, even though at a significantly low weight." This change was meant to maintain a focus on observable behavior rather than on subjective emotional states to address the fact that some individuals with AN do not admit to a fear of weight gain. The wording of the third criterion, related to body image, has been altered to again emphasize the nonvolitional nature of AN, with the phrase "denial of the seriousness of the low body weight" changed to "persistent lack of recognition of the seriousness of the current low body weight." This change was made to address the misperception, implied in the word *denial,* that individuals with AN are aware of but intentionally do not acknowledge the seriousness of low body weight. The fourth criterion, pertaining to amenorrhea, has been eliminated altogether. A significant minority of women have symptoms that meet all of the criteria for AN but menstruate occasionally, or are taking oral contraceptives or are postmenopausal. These individuals' presentations will now meet criteria for AN in DSM-5, whereas the symptoms were considered to be classified as EDNOS in DSM-IV. Finally, the subtyping of AN into restricting and binge-eating/purging subtypes remains in DSM-5.

Box 5. DSM-5 Diagnostic Criteria for Anorexia Nervosa

A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. *Significantly low weight* is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
B. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Coding note: The ICD-9-CM code for anorexia nervosa is **307.1,** which is assigned regardless of the subtype. The ICD-10-CM code depends on the subtype (see below).

Specify whether:

(F50.01) Restricting type: During the last 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.

(**F50.02) Binge-eating/purging type:** During the last 3 months, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Specify if:

In partial remission: After full criteria for anorexia nervosa were previously met, Criterion A (low body weight) has not been met for a sustained period, but either Criterion B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) or Criterion C (disturbances in self-perception of weight and shape) is still met.

In full remission: After full criteria for anorexia nervosa were previously met, none of the criteria have been met for a sustained period of time.

Specify current severity:

The minimum level of severity is based, for adults, on current body mass index (BMI) (see below) or, for children and adolescents, on BMI percentile. The ranges below are derived from World Health Organization categories for thinness in adults; for children and adolescents, corresponding BMI percentiles should be used. The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and the need for supervision.

Mild: BMI ≥ 17 kg/m^2
Moderate: BMI 16–16.99 kg/m^2
Severe: BMI 15–15.99 kg/m^2
Extreme: BMI < 15 kg/m^2

Changes to the criteria for bulimia nervosa (see Box 6) include reducing the minimum frequency of the binge criteria from at least two to at least one episode per week for 3 months. In addition, the subtyping of BN into purging and nonpurging types has been eliminated. With the inclusion of BED in DSM-5, the nonpurging subtype of BN is no longer recognized as a distinct subtype, and individuals previously diagnosed with BN, nonpurging subtype, would now be diagnosed as having BED. Finally, the word "purging" has been replaced by "inappropriate compensatory behaviors."

Box 6. DSM-5 Diagnostic Criteria for Bulimia Nervosa

307.51 (F50.2)

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
   1. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances.
   2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).

B. Recurrent inappropriate compensatory behaviors in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.

C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 months.

D. Self-evaluation is unduly influenced by body shape and weight.

E. The disturbance does not occur exclusively during episodes of anorexia nervosa.

Specify if:

In partial remission: After full criteria for bulimia nervosa were previously met, some, but not all, of the criteria have been met for a sustained period of time.

In full remission: After full criteria for bulimia nervosa were previously met, none of the criteria have been met for a sustained period of time.

Specify current severity:

The minimum level of severity is based on the frequency of inappropriate compensatory behaviors (see below). The level of severity may be increased to reflect other symptoms and the degree of functional disability.

Mild: An average of 1–3 episodes of inappropriate compensatory behaviors per week.

Moderate: An average of 4–7 episodes of inappropriate compensatory behaviors per week.

Severe: An average of 8–13 episodes of inappropriate compensatory behaviors per week.

Extreme: An average of 14 or more episodes of inappropriate compensatory behaviors per week.

The DSM-IV category of eating disorder not otherwise specified in DSM-IV is now referred to as *other specified feeding or eating disorder* and *unspecified feeding or eating disorder* in DSM-5. Included in these categories are a relatively small group of presentations that do not meet full criteria for any of the three full-syndrome eating disorders but that involve significant characteristic psychopathology and disordered eating. An example would be the case in which a woman at normal weight purges regularly.

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CHAPTER 30

Evidence-Based Psychological Treatments for Eating Disorders

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Substantial evidence supports the efficacy of psychological treatments for eating disorders. Most investigations have focused on syndromes characterized by binge eating—that is, bulimia nervosa (BN) and binge-eating disorder (BED). There are fewer studies of interventions for anorexia nervosa (AN), which is characterized by extreme dietary restriction and low body weight, although there is a growing evidence base documenting the efficacy of family therapy for younger individuals. In this chapter, we first consider evidence-based treatments for BN and BED and discuss efforts to disseminate efficacious treatments to patients in need of services. Next, we evaluate the evidence for psychological interventions for AN. Finally, we describe emerging directions for the treatment of eating disorders.

In light of the recent publication of DSM-5 (American Psychiatric Association 2013), it is necessary to note that virtually all psychological intervention studies to date have used the eating disorder criteria set forth in DSM-IV (American Psychiatric Association 1994). Importantly, changes to the criteria for the eating disorders are minimal and consequently are unlikely to affect the relevance of the available psychological treatment literature to the management of eating disorders diagnosed using DSM-5 criteria.

Interventions for Bulimia Nervosa

The most well-established intervention for BN is cognitive-behavioral therapy (CBT), which was adapted from CBT for

the treatment of depression (Beck et al. 1979). CBT for BN is based on Christopher Fairburn's (1985) model, which posits that stringent dieting to promote thinness precipitates binge eating. Binge eating is followed by compensatory behaviors that initially relieve concerns about potential weight gain, but soon thereafter lead to negative feelings, including shame and guilt, that serve to perpetuate dieting. In this context, maladaptive thoughts and beliefs regarding eating, shape, and weight serve to maintain the cycle of inappropriate dieting, binge-eating, and purging behaviors.

Traditional CBT consists of 15–20 sessions in three phases delivered over a period of about 6 months (Fairburn et al. 1993b). In the first phase, the emphasis is on regaining control of eating by adopting a pattern of regular meals and snacks, reducing dietary restriction, and using self-monitoring records to examine and understand the context and correlates of disordered eating, in particular maladaptive thoughts and beliefs. Homework assignments are used to practice and reinforce self-management skills. In the second phase, data from self-monitoring records are used more systematically to identify thoughts and beliefs related to eating behavior, and cognitive restructuring techniques designed to challenge and modify maladaptive cognitions are practiced. In the third and final phase, patients are encouraged to assume increasing responsibility for cognitive restructuring and self-management, progress is reviewed, and a relapse prevention plan is developed.

A substantial body of evidence supports the utility of CBT for BN delivered in individual sessions or groups. Across studies, CBT has been associated with significant reductions in binge eating and compensatory behaviors, as well as associated psychopathology, and BN remission rates of 30%–50% (Wilson et al. 2007). Moreover, CBT has demonstrated superiority relative to active control conditions such as interpersonal psychotherapy (IPT) in the short-term amelioration of bulimic symptoms (Agras et al. 2000; Fairburn et al. 1991). Although the quality of the extant studies has varied, comprehensive reviews (Berkman et al. 2006) and treatment guidelines (National Institute for Clinical Excellence 2004) have been published that indicate that CBT should be the first-line intervention for the treatment of BN. Notably, studies that have included both CBT and antidepressant medications have not yielded evidence that the addition of medication leads to greater improvements in eating disorder behavior or psychopathology over CBT alone (Walsh et al. 2004); however, adding an antidepressant to CBT may proffer additional advantages with regard to decreasing symptoms of depression (Walsh et al. 1997).

IPT also has demonstrated efficacy in the management of BN. Like CBT, IPT was adapted by Fairburn and colleagues (Fairburn 1997) for the treatment of eating disorders from the approach developed by Klerman et al. (1984) for the treatment of depression. IPT posits that depression occurs in an interpersonal context; the strategies of IPT target a specific current interpersonal problem area in the service of relieving depressive symptoms by increasing interpersonal effectiveness. Thus, IPT adapted for the treatment of BN is based on the observation that interpersonal difficulties are common and contribute to the maintenance of disordered eating behaviors. As noted, IPT was used as a control treatment in two major trials of CBT (Agras et al. 2000; Fairburn et al. 1991). In the first trial, results indicated that CBT was more

effective than IPT at reducing binge eating and compensatory behaviors (Fairburn et al. 1991), but differences between CBT and IPT were attenuated after 1- and 6-year follow-ups (Fairburn et al. 1993a, 1995). In the second trial—a larger, two-center study—findings were similar; that is, CBT was superior initially, but results of the treatments converged by 8- to 12-month follow-up (Agras et al. 1997). Thus, it appears that the longer-term benefits of CBT and IPT are equivalent but that the rate of improvement is slower for IPT. Despite these data documenting the utility of IPT, the evidence base for IPT is considerably smaller than that for CBT, which has demonstrated efficacy in many more studies from different centers.

Interventions for Binge-Eating Disorder

Binge eating is a hallmark of both BN and BED, but in the case of BED the recurrent and persistent binge eating occurs in the absence of regular compensatory behaviors. Given the similarities between the disorders, and because strategies used in CBT and IPT for BN focus on identifying and modifying the triggers for binge eating, it is unsurprising that CBT and IPT also have been used in the treatment of BED. CBT for BED (Fairburn et al. 1993b) has been adapted to reflect the fact that BED is strongly associated with obesity (Hudson et al. 2007), which is unsurprising given that overall dietary restraint is lower than that observed in individuals with BN, and the recurrent binge eating is not coupled with the compensatory behaviors seen in BN. Specifically, CBT for BED focuses on maladaptive beliefs and cognitions associated with being overweight or obese. Interventions focus on helping individuals with BED accept a larger than average body size, identifying and modifying maladaptive thoughts and beliefs about being overweight, and altering unrealistic expectations about weight loss. In contrast to CBT for BN, which focuses on reducing stringent dietary restraint, overweight or obese individuals with BED are encouraged to increase restraint by adopting a moderate, healthy eating plan. CBT is considered to be the treatment of choice for BED, as it is for BN, because of the number of studies providing empirical support for its utility (National Institute for Clinical Excellence 2004) and binge eating remission rates of approximately 50% (Wilson et al. 2007).

Evidence also supports IPT in the treatment of BED, based on the hypothesis that interpersonal problems maintain aberrant eating. CBT and IPT offered in a group format have been shown to lead to equivalent improvements in remission at the end of treatment (79% and 73% for CBT and IPT, respectively) and at 1-year follow-up (59% and 62%, respectively) (Wilfley et al. 2002). Notably, IPT does not address eating disorder symptoms specifically, and thus may be a differentially effective approach for patients who do not want a symptom-focused treatment.

Obese individuals with BED typically want to lose weight, and BED is common in obesity treatment–seeking samples (Marcus and Levine 2004). Furthermore, the behavioral self-management strategies used in behavioral weight loss (BWL) programs are very similar to those used in the first phase of CBT. Consequently, there has been considerable interest in the relative efficacy of CBT and BWL for obese patients with BED. Recently, Grilo et al. (2011) examined the impact of CBT, BWL, and CBT plus BWL offered sequentially. CBT was associated with higher rates of binge eating remission at 1-year

follow-up (51% and 36% for CBT and BWL, respectively), whereas BWL yielded significantly higher rates of modest weight loss during active treatment (0.9% decrease in body mass index [BMI] for CBT, compared with 2.1% for BWL). The sequential treatment did not confer additional benefits. Finally, independent of intervention condition, sustained remission from binge eating was associated with greater decreases in BMI, suggesting that the elimination of aberrant overeating may promote weight decreases over time.

Some studies are investigating the utility of guided self-help approaches to implementing CBT for BED in which a CBT self-help manual (Fairburn 1995) is provided with guidance and support from a mental health provider. Wilson and Zandberg (2012) have summarized these studies and documented that, overall, CBT-guided self-help can be as effective as specialty care treatment.

Findings from a study by Wilson et al. (2010) provide a reasonable summary of current knowledge about evidence-based treatment of BED. In this investigation, overweight individuals with BED were randomly assigned to receive IPT (20 sessions), BWL (20 sessions), or CBT-guided self-help (10 sessions) provided over a 6-month period. There were no significant differences among groups at the end of treatment in binge eating remission; however, at 2-year follow-up, IPT and CBT were associated with similar rates of binge eating remission (approximately 60%), which were significantly higher than the rate of remission observed for BWL (approximately 40%). Although participants assigned to BWL initially lost more weight, there were no differences among intervention conditions in BMI at 2-year follow-up. There was no relationship between sustained binge eating abstinence and percentage of weight loss at 2-year follow-up, but binge-eating remission was associated with a greater likelihood of losing at least 5% of initial body weight. In summary, either CBT (or CBT-guided self-help) or IPT is more effective than BWL for BED patients. Nevertheless, in the Wilson et al. (2010) study, attrition from CBT-guided self-help (30%) was significantly higher than attrition from IPT (7%), and guided self-help was rated as less suitable by participants, despite evidence for similar efficacy. Thus, although CBT-guided self-help appears to be a reasonable front-line treatment for BED, more intensive treatments may be indicated for complicated or chronic patients.

Dissemination of Evidence-Based Treatments for Bulimia Nervosa, Binge-Eating Disorder, and Binge Eating

Along with widespread acknowledgment that CBT is efficacious in the treatment of BN and BED, there is recognition that access to this evidence-based psychotherapeutic intervention is limited (Wilson and Zandberg 2012). As indicated by studies on the use of CBT-guided self-help for BED described in the previous section of this chapter, there is a growing body of work documenting the utility of guided self-help interventions for BN (Sysko and Walsh 2008) and BED. Indeed, the National Institute for Clinical Excellence (2004) guideline acknowledges with a grade of B that CBT-guided self-help is a reasonable first step in the context of a stepped care approach for the treatment of BN and BED.

Striegel-Moore et al. (2010) documented that an eight-session version of CBT-guided self-help for recurrent binge eating (BED, BN, or recurrent binge eating that did not meet DSM-IV criteria for BN or BED) delivered during a 3-month period can be implemented by clinicians with master's degrees in the context of a large health maintenance organization. In this randomized controlled trial (RCT) of guided self-help compared with treatment as usual, results indicated that CBT was associated with significantly higher rates of binge eating abstinence at 52 weeks (64.2%) than treatment as usual (44.6%). Importantly, a cost-effectiveness analysis, which evaluated costs to both patients and the health plan, has provided preliminary evidence that the intervention was associated with lower net costs than treatment as usual (Lynch et al. 2010) and bolstered the argument for widespread dissemination of CBT-guided self-help.

Some researchers have begun to examine differing modes of intervention delivery, including Internet-based guided self-help (Ljotsson et al. 2007) and the combination of an Internet-based approach with weekly or biweekly e-mail contact from therapists (Sánchez-Ortiz et al. 2011). In addition, investigators have begun to evaluate the use of alternative modalities in combination with traditional interventions. For example, Bauer et al. (2012) used tailored text messages with the goal of consolidating treatment gains obtained during inpatient treatment for BN or BN-related disorder. Efforts to implement and evaluate efficacious, cost-effective, and accessible interventions for BN and BED are a public health priority, and the new generation of work to develop novel dissemination modalities offers hope that evidence-based treatment will become widely available.

Interventions for Anorexia Nervosa

The evidence base related to the psychological treatment of AN is much weaker than that for BN and BED. First, because the starvation and consequent emaciation that characterize the disorder affect cognition, the utility of psychotherapy in acutely ill individuals is questionable. Second, starvation increases medical risk, and patients with AN often require supervised refeeding provided in a residential, inpatient, or day hospital setting to restore adequate nutrition and body weight to a healthy range. Third, given the marked fear of gaining weight or becoming fat associated with the disorder, individuals with AN frequently are resistant to participating in treatment in which achieving a healthy body weight is regarded as essential to recovery. Finally, AN is the least common of the eating disorders (Hudson et al. 2007), which poses a challenge for designing and implementing RCTs. Nevertheless, there is increasing evidence that family therapy is efficacious in the treatment of adolescent AN, and a small number of studies suggest the utility of CBT in the treatment of adult AN.

Several controlled trials have documented the utility of the Maudsley model, an approach to family therapy that was tailored to the needs of adolescents with AN (Lock and le Grange 2005; Russell et al. 1987). Specifically, the pragmatic, symptom-focused approach is delivered in 15–20 conjoint family sessions over a period of 6–12 months. The therapist serves as consultant to the family, and in the first phase of treatment focuses on empowering parents to assume responsibility for refeeding the adolescent with

AN, and providing coaching to minimize factors that interfere directly with normalization of eating. In the second phase, the therapist helps parents to return responsibility for eating back to the adolescent. In the third and final phase, the work focuses on helping the adolescent to develop a healthy identity and the family to negotiate the developmental transitions of adolescence. Initial studies documented the utility of family therapy for younger, recent-onset patients with AN in consolidating treatment gains achieved during hospitalization (Eisler et al. 1997; Russell et al. 1987), with impressive recovery rates of up to 90%. Subsequent controlled trials (Eisler et al. 2000) also have yielded positive results.

Nevertheless, Wilson et al. (2007) noted that favorable findings from trials of the Maudsley model may reflect the fact that adolescents have more favorable treatment outcomes than older patients, regardless of the treatment provided, and that few investigations have compared the intervention to alternative models of treatment. Moreover, Wilson et al. questioned the recommendation of conjoint family therapy, in light of findings that suggest that separated therapy in which parents and adolescents are seen in separate sessions is superior to conjoint treatment, particularly for families with high levels of expressed emotion (Eisler et al. 2000). Despite limitations in the current evidence base, a recent meta-analysis evaluating the efficacy of family-based treatment of adolescents with eating disorders, which included four studies that targeted AN, concluded that family therapy for adolescents with AN is superior to individual treatment and should be recommended as the first line of treatment (Couturier et al. 2013).

As we have noted, there is a paucity of literature examining the effects of psychological treatments for adults with AN. The best studied intervention is CBT, which has been included as one of the treatment conditions in a number of small clinical trials. For example, in a widely cited study, Pike et al. (2003) compared the utility of CBT delivered over 1 year versus nutrition counseling for adult patients after being released from hospital treatment of AN. Survival analyses documented that CBT was associated with longer periods without relapse than nutrition counseling, and more CBT patients achieved a good outcome. Another investigation examined the utility of three therapies—CBT, IPT, and nonspecific supportive clinical management—in the treatment of outpatients with AN (McIntosh et al. 2005). Results showed that clinical management was superior to IPT in global clinical outcome, while CBT was associated with favorable changes that were intermediate, but not significantly different from either of the other interventions.

Although preliminary data suggest the potential utility of CBT for AN (Wilson et al. 2007), the aforementioned studies highlight the problems in the extant literature. First, sample sizes have been small (*N*s=33 and 56 in the Pike et al. 2003 and McIntosh et al. 2005 studies, respectively). Many studies have not compared CBT with an active psychotherapeutic intervention, limiting the ability to draw firm conclusions. For example, the Pike et al. (2003) study evaluated the relative efficacy of CBT and nutrition counseling, which had an unacceptably high rate of treatment failure (73%), confounding comparisons between intervention conditions. Finally, overall treatment gains have been disappointing. For example, in the McIntosh et al. (2005) study, 70% of participants either did not complete treatment or failed to benefit from interven-

tion. In summary, no compelling evidence currently supports any particular brand of psychotherapy for adults with AN.

Alternative and Emerging Directions for Treatment of Eating Disorders

Several lines of work may ultimately yield evidence-based options for the psychotherapeutic armamentarium for individuals with eating disorders. In this section, we briefly discuss transdiagnostic approaches, interventions incorporating principles from third-generation CBTs, and preliminary studies of theory-based interventions for AN.

In recognition that all eating disorders appear to have similar maintaining factors, Fairburn et al. (2008) developed an enhanced CBT (CBT-E) to address a fuller range of factors that serve to maintain disordered eating. Two versions of CBT-E have been compared in an RCT, which included patients with an eating disorder who were not underweight (Fairburn et al. 2009). One version of CBT-E focused only on eating disorder symptoms, and the other included modules focusing on additional correlates of disordered eating, namely mood intolerance, perfectionism, low self-esteem, and interpersonal difficulties. No difference in outcome was found between the two types of CBT-E, although there was some indication that more complex patients had greater benefit from the version of CBT-E with the additional modules. Nevertheless, rates of binge and purge abstinence at the end of treatment (38.8% and 42.6% for the eating disorder–focused and the expanded versions of CBT-E, respectively) appear to be similar to those observed in trials of the original CBT for BN. A recent uncontrolled trial of 40 weeks of CBT-E in the treatment of adults with AN (Fairburn et al. 2013) indicated that this intervention has promise for the 64% of patients who completed treatment. However, additional research is needed to evaluate whether the enhanced version of CBT is efficacious in treating AN or BED, and whether enhanced CBT confers benefits over and above those seen with the original CBT.

Numerous studies have examined the potential utility of so-called third-generation behavioral interventions in the treatment of disordered eating. Third-generation interventions include dialectical behavior therapy (DBT; Linehan 1993), acceptance and commitment therapy (ACT; Hayes et al. 1999), and mindfulness-based cognitive therapy (MBCT; Segal et al. 2002). In contrast to earlier cognitive-behavioral approaches, third-generation therapies emphasize the context and function of psychological experiences rather than symptoms per se. These interventions incorporate strategies such as mindfulness, acceptance, and values that have demonstrated utility in the management of problems characterized by emotional dysregulation and avoidance. Initial studies have examined DBT skills training for BN (Safer et al. 2001) and BED (Telch et al. 2001), and DBT for individuals with comorbid eating disorder and personality disorder (Palmer et al. 2003), with promising short-term results. Furthermore, ACT was examined in a case series of patients with AN (Berman et al. 2009), and MBCT was examined in a case study of binge eating (Baer et al. 2005). In the absence of full-scale RCTs that include active comparison conditions, additional study is required to document the efficacy of these approaches for the treatment of eating disorders.

Finally, in recognition of the lack of efficacious interventions for adults with AN, the National Institute of Mental Health has funded several small studies focusing on the development and evaluation of new psychological interventions. These investigations, which focus on a couples approach to the management of AN (Bulik et al. 2011), the application of exposure and response prevention to AN (Steinglass et al. 2011), an AN-specific psychotherapeutic approach to reduce emotion avoidance and promote a values-driven life (Wildes and Marcus 2011), and the utility of cognitive remediation as an adjunctive intervention in the treatment of AN (Tchanturia and Lock 2011), may yield important findings that will inform subsequent clinical trials and lead to efficacious interventions for adults.

Conclusion

The strength of the evidence base supporting psychological interventions for eating disorders varies by disorder. There is excellent support for the efficacy of CBT in the treatment of BN, and IPT also has good evidence. There is good support for CBT in the treatment of BED, as well as some support for IPT and DBT. In the case of AN, family-based therapy is recommended for younger patients, whereas for older patients, for whom the evidence base is weak, expert management and CBT may be useful. Nevertheless, critical challenges remain.

As noted universally, a considerable proportion of individuals do not benefit sufficiently from even the most effective interventions. There also is relatively little information about combining psychotherapy with medication, and limited understanding of treatment moderators or mediators, which would facilitate matching patients and interventions. Finally, more work is needed to develop and evaluate scalable versions of efficacious psychological interventions.

Most of the current psychotherapeutic interventions for eating disorders have been adapted from approaches used in the treatment of other psychiatric disorders, which may well reflect that there is overlap in the mechanisms that maintain all psychological disturbances, such as maladaptive thoughts and beliefs, interpersonal conflict, or mood reactivity. Nevertheless, ongoing work to identify the specific neurobiological underpinnings of eating disorders, especially AN, may lead to the identification of novel treatment targets and eating disorder–specific therapies.

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CHAPTER 31

Pharmacological Treatment of Eating Disorders

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Relatively few significant advances have occurred in the pharmacological management of eating disorders in recent years. In patients with anorexia nervosa (AN), pharmacotherapy studies have failed to find significant benefit across several medication classes and numerous controlled trials. Currently, no evidence-based pharmacological recommendations can be made for the treatment of AN. In bulimia nervosa (BN), pharmacotherapy trials have been more positive, and fluoxetine has been approved by the U.S. Food and Drug Administration (FDA) for this indication. Additional research on combination pharmacotherapy and augmentation strategies for treating partial responders and nonresponders to medications also should be considered. In binge-eating disorder (BED), medications from numerous classes have resulted in reductions in binge-eating frequency. Few trials, however, have resulted in meaningful weight loss, which is generally desired by BED patients who seek treatment. Additional research is needed in the pharmacotherapy of all of the eating disorders, especially the pharmacological treatment of AN.

Pharmacotherapy of Anorexia Nervosa

Despite the efforts of researchers over the past 30 years to identify useful pharmacological agents for AN, no drugs currently have approval by the FDA for this condi-

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tion. Moreover, there is a lack of evidence-based recommendations for drug treatment in AN. Pharmacological agents were generally selected for investigation on the basis of their ability to modify conditions that are frequently comorbid with AN, such as mood and anxiety disorders, or their ability to stimulate weight gain. A review of the pharmacotherapy literature leads to the conclusion that pharmacotherapy is not a useful treatment modality for most patients with AN.

Antidepressants

Historically, antidepressants received significant attention for the treatment of AN. Early on, the tricyclic antidepressants (TCAs) amitriptyline and clomipramine were investigated in controlled trials for their ability to promote weight regain among acutely ill hospitalized patients with AN (Biederman et al. 1985; Halmi et al. 1986; Lacey and Crisp 1980). The TCAs previously had been shown to result in weight gain as well as to improve mood in other conditions, making these drugs reasonable options for investigation in AN. Overall, however, treatment with the TCAs did not improve the rate of weight regain or appreciably improve mood among AN inpatients. The TCAs can also lead to serious adverse events, as well as fatality in overdose.

Although the selective serotonin reuptake inhibitors (SSRIs) are generally considered weight neutral, their efficacy in numerous psychiatric conditions led to their investigation in the treatment of AN. In a controlled trial, Attia et al. (1998) examined the ability of fluoxetine versus placebo to accelerate weight regain in 33 inpatients over 7 weeks at a maximum dosage of 60 mg/day. Although the drug was well tolerated, it failed to improve weight gain or mood beyond that observed with placebo. Kaye et al. (2001) examined whether fluoxetine would prevent relapse among 39 outpatients with AN. This continues to be the only trial to show significant benefit for an antidepressant in the treatment of AN. After 52 weeks, more patients continued to take fluoxetine (10/16) than continued to take placebo (3/19), and drug-treated patients had higher weights and reduced eating disorder symptoms compared with those given placebo. Later, Walsh et al. (2006) performed a larger, similar study to examine whether fluoxetine prevents relapse in AN. Outpatients with AN were randomly assigned to receive fluoxetine, with a target dosage of 60 mg/day (n=49), or placebo (n=44). This study failed to replicate the findings by Kaye et al. (2001) and found no difference between groups on time to relapse or on depressive symptoms. Data available at the present time suggest that antidepressants are not effective for the treatment of AN.

Antipsychotics

In the early 1980s, Vandereycken and colleagues (Vandereycken 1984; Vandereycken and Pierloot 1982) examined the first-generation agents pimozide and sulpiride for the treatment of AN inpatients. After these drugs failed to improve outcome, there was little research interest in the treatment of AN with antipsychotics until case reports of successful treatment of AN patients with second-generation antipsychotics (SGAs) started to emerge in the late 1990s. Researchers began to examine whether the weight gain observed with several of the SGAs could offer therapeutic benefit in the treatment of AN. In addition, some have suggested that the distorted thinking that is often observed in patients with AN resembles delusional thinking, which

may improve with antipsychotic therapy (Kraus et al. 1999). Numerous positive case series and uncontrolled trials resulted in several randomized controlled trials of various SGAs for the treatment of AN. Most recently, there has been a review published on the topic of antipsychotic therapy for treatment of AN (McKnight and Park 2010), as well as two meta-analyses (Kishi et al. 2012; Lebow et al. 2013). These meta-analyses and conclusions from the review concur that the antipsychotic literature in AN reveals a lack of efficacy for the SGAs. The data fail to show a significant improvement in weight or body mass index with SGA treatment over placebo. However, subgroups of patients with AN may benefit from antipsychotic therapy, and larger studies are needed to examine this issue.

Other Agents

Numerous agents aside from antidepressants and antipsychotics have been investigated for the treatment of AN. These include lithium, zinc, tetrahydrocannabinol, naltrexone, clonidine, recombinant human growth hormone, metoclopramide, domperidone, and cisapride, none of which has been established as a viable therapeutic approach for most patients, with the possible exception of zinc supplementation. Other reviews have addressed these data in more detail (Crow et al. 2009; Steffen et al. 2006).

Summary

Some controlled data support the use of zinc in AN. Given that zinc is relatively benign in the doses administered in the AN trials, this agent may be considered for use in some patients. The other pharmacological agents discussed are not appropriate for the clinical treatment of AN at the present time due to lack of efficacy or poor tolerability in patients with AN. Reasons for this striking lack of efficacy across medication classes in treating AN require additional exploration.

Pharmacotherapy for Bulimia Nervosa

BN is currently the only eating disorder for which the FDA has approved a medication, fluoxetine. Other antidepressants have also shown efficacy in the treatment of BN. More recently, topiramate and ondansetron have been shown to be efficacious in controlled trials. Research still needs to address whether patients who do not achieve remission from BN symptoms are adequately treated with pharmacotherapy or whether augmentation or combination strategies should be employed for these patients.

Antidepressants

In reviewing the agents used to treat BN, one finds that the bulk of the studies involve antidepressants, primarily SSRIs (Bacaltchuk and Hay 2003). The use of these drugs would seem to be justified, because the lifetime comorbidity of depression in patients with BN has been reported to be close to 50% (Hudson et al. 2007). Nevertheless, the efficacy of antidepressants appears to not be dependent on the presence of mood symptoms in the patient with BN.

Fluoxetine carries an indication for treating BN at dosages up to 60 mg/day (Fluoxetine Bulimia Nervosa Collaborative Study Group 1992). Other antidepressants, including desipramine, imipramine, milnacipran, and trazodone, have demonstrated efficacy. Two reversible monoamine oxidase type A inhibitors (moclobemide and brofaromine) and lithium have been investigated, with no demonstrated efficacy. Lastly, bupropion is

contraindicated in BN because of the high rate of seizures. Several shortcomings are associated with these studies. First, much of the data are from small studies of short duration. Second, binge eating and purging abstinence rates often are not reported. Of the studies that do report abstinence rates, the mean is 22.6% (Hay and Claudino 2012). Third, the dropout rate for many trials is quite large, ranging anywhere from 25% to 87% of subjects across trials. Fourth, limited maintenance data are reported. The longest study, which lasted 52 weeks, found a benefit of fluoxetine over placebo; however, 87% of the subjects dropped out (Romano et al. 2002). Lastly, very few data have been generated regarding the optimal course of treatment for those who do not achieve abstinence. Exploration of augmentation or switching strategies has not been performed; this lack of data is distressing considering the low abstinence rate. The affective disorder data in general support a treatment goal of complete remission of symptoms, because the patients who are depressed who do not achieve remission have a poor course of illness with relapse and progression to chronic refractory depression (Judd et al. 1998; Paykel et al. 1995). In light of the comorbidity with mood disorders, this phenomenon may be operative in BN also.

Other Agents

Other than antidepressants, a small variety of drugs, including topiramate, ondansetron, and flutamide (androgen receptor antagonist), have demonstrated benefit in controlled studies of patients with BN. Other agents have been explored in small controlled trials or in case reports or series. Although these studies may not be at the antidepressants' level of evidence, they can be looked at as proof-of-concept studies that may provide alternatives for refractory patients and further research.

Faris et al. (2000) conducted a double-blind placebo-controlled study in 26 subjects over 4 weeks who were randomly assigned to receive the serotonin 5-HT_3 antagonist ondansetron or placebo. Ondansetron demonstrated a significantly greater improvement in the number of normal meals consumed and time spent engaging in bulimic behaviors. The mean binge eating/vomiting frequency was found to be 13.2 per week in the placebo group and 6.5 per week in the ondansetron group.

Sundblad et al. (2005) compared the androgen receptor antagonist flutamide with citalopram, flutamide plus citalopram, and placebo in 46 patients over 12 weeks. Overall, the active treatments were found to be superior to placebo. The percentage reduction in episodes of binge eating was significant for both of the groups given flutamide but not for the groups given only citalopram or placebo. Both drugs were well tolerated. However, caution needs to be exercised because flutamide may exert teratogenic effects; therefore, only subjects using reliable contraceptive techniques should be candidates for treatment. Also, the possible effect of flutamide on liver function requires monitoring of liver enzymes during treatment.

Topiramate is an anticonvulsant that enhances γ-aminobutyric acid type A ($GABA_A$) activity, antagonizes AMPA/kainate glutamate receptors and weakly inhibits carbonic anhydrase. Two double-blind, randomized controlled trials have been performed with topiramate (Hoopes et al. 2003; Nickel et al. 2005). Topiramate was used at dosages ranging from 25 to 400 mg/day, and approximately 60 subjects were entered into each study. The duration of each study was 10 weeks. Nickel et al. (2005) reported a 50% reduction in

binge eating and/or purging in 36.7% of the topiramate group versus 3.3% in the placebo group. Hoopes et al. (2003) reported a 44.8% reduction in binge eating and/or purging days for topiramate versus 10.7% for placebo. Also, the remission rate for binge eating and/or purging days was reported as 22.6% for topiramate versus 6.1% for placebo, which did not reach significance. Topiramate was also found to induce greater weight loss compared to placebo. Both studies reported that subjects tolerated the medication well, with the adverse effects of fatigue, flulike symptoms, paresthesias, sedation, dizziness, and headache occurring. However, cognitive impairment has been commonly reported with topiramate and may affect compliance. Adverse events reported in >10% of subjects include somnolence, dizziness, fatigue, nervousness, ataxia, psychomotor slowing, speech problems, memory difficulties, and confusion (Lexi-Comp, Inc., http://www.lexi.com/). Lastly, because topiramate is a teratogen, women of childbearing age should be educated as to the need for contraception.

Stimulants have also been examined and represent a somewhat unusual class of drugs for the treatment of BN. Dukarm (2005) reported the case studies of six patients with comorbid BN and attention-deficit/hyperactivity disorder (ADHD) who were treated with dextroamphetamine. The rationale for studying a stimulant medication was that BN and ADHD share key features, including impulsivity and low self-esteem. All six patients reported complete abstinence from binge eating and purging after treatment with psychostimulants and were reported to tolerate the medication well. Sokol et al. (1999) noted that many of the BN patients who are poor responders to psychotherapy and antidepressants also have cluster B personality disorders. They suggest that the symptomatology, such as impulsivity, of BN patients who have a comorbid cluster B disorder is similar to that of patients with ADHD. Several studies using the opioid receptor antagonist naltrexone have been reported (e.g., Marrazzi et al. 1995; Mitchell et al. 1989), and showed conflicting results, which may have been due to dosage differences.

Summary

Antidepressant treatment is the most studied pharmacotherapy, and the SSRIs occupy a central role. Antidepressants are moderately effective in reducing binge eating and purging frequency and some of the psychological symptoms, but compliance is generally poor. None of the treatments examined to date have produced an acceptable level of abstinence. A variety of other agents have been reported to have efficacy in the treatment of BN. However, many are single studies, have a small number of subjects, and are of short duration. Further research exploring the efficacy and tolerability of these treatments is needed. Also, very few data have been generated regarding treatment options for patients who do not achieve abstinence. Exploration of augmentation and switching strategies in unresponsive or partially responsive patients needs to be conducted. Further works in this area could lead to an improvement in outcome and increase the number of patients who achieve remission of this illness.

Pharmacotherapy of Binge-Eating Disorder

In considering drug treatments for patients with BED, the clinician must delineate each patient's goals in seeking treatment, as well as the goals that the treating practitioner is targeting and believes are

realistic. Many patients seeking therapy for BED are primarily interested in weight loss, although most of the treatments that have been developed for BED have focused on the control of eating behavior. An assumption early on in the development of this treatment literature was that if the patients learned techniques to control their binge eating, they would subsequently experience a decrease in caloric intake and lose weight. However, early studies failed to support this assumption, and it became clear that the best outcome with most pharmacological interventions was at most a modest weight loss, but more likely stability in weight, and perhaps lack of further weight gain. Consequently, additional agents have been explored in the treatment of BED, and more recently there has been an emphasis on using either drugs that suppress binge eating and result in weight loss or drugs that can be combined to achieve both of these ends. Notably, no agents have received FDA approval for the treatment of BED. Given that most of the agents we will be considering in this section are now available in generic form, pharmaceutical firms have little motivation to continue exploring the development of these compounds to obtain FDA approval for BED. Therefore, clinicians are currently left with using agents that have been tested in only relatively small samples, and often in relatively brief trials, when patients with BED have been studied. Some of the results, however, are positive and encouraging. Individuals who are particularly interested in this area are referred to several other excellent reviews that have appeared in the literature in the last several years (Aigner et al. 2011; McElroy et al. 2012).

Early on, most of the treatments that were applied to the treatment of patients with BED reflected prior experiences in the treatment of patients with BN. This is logical given that both patients with BN and those with BED experience eating binges during which they feel a sense of loss of control. The most important difference is that patients with BED do not follow the behavior with compensatory behaviors, as is seen in those with BN. However, suppression of binge eating was the target in early trials. As the field has progressed, researchers and clinicians have turned to agents that have also been shown to result in weight loss.

Antidepressants

The first agents that were systematically applied to patients with BED were the traditional TCAs and later the SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and norepinephrine reuptake inhibitors (NRIs). These trials reflected both the experience in treating patients with BN and the fact that many patients with BED also evidenced prominent symptoms of depression.

Over time, various antidepressants have been used, at times in comparison to placebo and at other times in comparison to other drug therapy, and in some designs augmented with other interventions, such as dietary counseling (Grilo et al. 2005b; McElroy et al. 2012). The results of the antidepressant drug studies are summarized in Table 31–1. In those trials, there was a substantial effect on binge eating frequency, which was quite encouraging; however, patients rarely experienced substantial loss of weight. Again, as summarized in Table 31–1, most of the SSRIs have been used, including escitalopram, fluvoxamine, fluoxetine, and sertraline. In contradistinction to the TCA studies, in some of these studies, there was a significant, albeit modest, reduction in weight, although this was in-

consistent (Aigner et al. 2011). Given the relative lack of side effects of these classes of drugs, and given that at times their use results in some weight loss, the SSRIs became the agents of choice.

TABLE 31–1. Drug treatment for binge-eating disorder

Class	Drug	Binge eating reduction	Weight loss	Side effects/ intolerance
Antidepressants				
TCAs	Imipramine	++	+/−	++
	Desipramine	++	+/−	+
SSRIs	Citalopram	++	+	+/−
	Escitalopram	++	+	+/−
	Fluvoxamine	++	+	+/−
	Sertraline	++	+	+/−
	Fluoxetine	++	+	+/−
NRIs	Atomoxetine	++	+	+/−
SNRIs	Venlafaxine	++	+	+/−
	Duloxetine	++	+	+/−
Other agents				
Orlistat	Orlistat	+/−	++	+
Antiepileptics	Topiramate	++	+++	++
	Zonisamide	++	+++	++

Note. Insufficient data: baclofen, sodium oxybate, lamotrigine, acamprosate.
NRI=norepinephrine reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.
+/−=minimal/few; +=modest/mild; ++=significant/moderate; +++=substantial/severe.

While the results suggest significant improvements with antidepressants in terms of binge eating, they also suggest that although the mechanism may involve serotonergic functioning, other neurotransmitter systems are likely involved. Also, some of the trials documented significant improvement in depressive symptoms in patients with BED.

Antiepileptic Agents

Early in the study of certain agents in the treatment of epilepsy, some patients were noted to experience weight loss, which could be seen as a problem or a benefit depending on the patient's baseline weight. These agents have since been used in a number of studies in individuals who are overweight or obese, and more recently in individuals with BED. As can be seen in Table 31–1, these drugs do result in reductions in binge eating and in weight that are usually superior to those of most of the other interventions listed (McElroy et al. 2003, 2004). Other work has examined the possibility of combination therapy. For example, Claudino

et al. (2007) could not find benefit in adding the antiepileptic drug topiramate to cognitive-behavioral therapy (CBT) in terms of reduction of binge eating frequency but did find benefits in terms of weight loss. The most frequently used antiepileptic drug has been topiramate, but work using zonisamide has had similar results. However, the research in this area suggests that these medications need to be used cautiously because of possible associated side effects and toxicity.

Other Agents

Sibutramine was shown to result in both a reduction in binge eating frequency and weight loss in controlled trials (Appolinario et al. 2003; Wilfley et al. 2008); however, this drug is no longer marketed because of toxicity concerns. Another agent that is no longer marketed is D-fenfluramine, which was shown to result in substantial decrements in binge eating.

A lipase inhibitor, orlistat, which has FDA approval for the treatment of overweight and obese patients, has also been used in individuals with BED, targeting weight loss as opposed to binge eating frequency. Positive effects have been documented, including when the medication is used as an adjunct to CBT (McDuffie et al. 2004) and in combination with other interventions including CBT self-help therapy (Chanoine et al. 2005; Grilo et al. 2005a). The exact mechanism underlying the effect is not clear, because orlistat usage results in the malabsorption of fat that has been ingested in the diet, and the ingestion of excessive fat can result in unpleasant gastrointestinal side effects. Whether the effect results from the malabsorption of fat and/or the propensity for those treated to avoid high fat in the diet to prevent the side effects involved is unclear.

A number of other agents have been used in isolated or small trials. These have included baclofen (Broft et al. 2007), lamotrigine (Guerdjikova et al. 2009), and acamprosate (McElroy et al. 2011a). The trials using the latter two agents failed to find benefit in the primary analysis. However, in one open-label trial, sodium oxybate was shown to benefit patients (McElroy et al. 2011b).

Summary

A variety of agents that have been tried experimentally have resulted in significant improvements in binge eating frequency, although most of these trials were of relatively brief duration and had relatively small sample sizes. Lack of significant reductions in weight has been a problem with the TCAs and to some extent with the SSRIs, the SNRIs, and the NRIs. Orlistat seems to have some effect on weight but not on binge eating, and very limited data exist on baclofen, sodium oxybate, lamotrigine, and acamprosate. The two antiepileptic agents topiramate and zonisamide appear to have robust effects on reductions in binge eating frequency and on weight loss compared to the other agents that have been used; however, these agents can be difficult to use because of their possible side effects and toxicity, and they must be used cautiously, often in dosages that are significantly lower than those employed in patients with epilepsy.

Conclusion

Additional research is needed in eating disorder pharmacotherapy. An improved understanding of the reasons why pharmacological approaches have been unsuccessful in AN is imperative. Additional

research in BN on pharmacological augmentation options or combination therapy should be explored; and medications that produce weight loss should be examined for efficacy in patients with BED. Overall, there are effective pharmacological options for the treatment of BN and BED, although effective AN pharmacotherapy remains elusive.

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CHAPTER 32

Intensive Treatment for Eating Disorders

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Eating disorders, including anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED), are serious psychiatric illnesses. The morbidity and mortality rates for these disorders are among the highest seen for any psychiatric illness. The serious and complex nature of these illnesses and their associated features have led to the development of psychosocial and medical treatments that utilize a range of treatment settings. Intensive treatments have evolved in efforts to interrupt maladaptive eating and associated behaviors and to manage the medical complications that are commonly present.

In this chapter, we introduce and describe intensive treatment for eating disorders and review the evidence for this approach across a range of treatment settings. In addition, we address some of the treatment challenges specific to intensive treatment for eating disorders, with attention to the treatment of the patients who are not voluntary participants in treatment.

Intensive Treatment Settings

Intensive treatment for eating disorders generally refers to treatment that includes multiple treatment modalities that are incorporated into a schedule of several visits per week and several hours for each visit. Supervised meals and group-based interventions are core components for most intensive treatment programs for eating disorders. The treatment aims of

intensive treatments generally include behavioral change and improved measures of physiological and psychological function. Programs that offer intensive treatment use behavioral management strategies that are implemented through supervised meals, as well as individual and group therapy. The various treatment settings within which intensive treatment may be delivered include intensive outpatient programs (IOPs), partial hospital programs (PHPs), residential treatment centers (RTCs), and inpatient programs.

Intensive Outpatient Programs

An IOP generally is a nonresidential group-based treatment that includes several hours of treatment per visit, usually with at least three visits per week. In IOPs that specialize in eating disorders, counseling and education are generally offered together with a supervised meal. An IOP may be considered for individuals who are able to function in a school, work, or home environment but who need more structure than what traditional outpatient interventions can offer. IOP treatment is commonly used to transition a person from a higher level of care or to help increase supervision to decrease the likelihood that a person will require a higher level of care in the future.

Partial Hospital Programs

PHPs, or day treatment programs, offer more hours of weekly treatment than do IOPs. PHPs became a formally recognized treatment setting category in 1988 when the United States included this level of care in the federally granted Medicare program. PHPs are specifically designed for the active treatment of a serious mental illness. A PHP is a distinct, organized, intensive ambulatory treatment service of less than 24-hour daily care. For some patients, PHPs may shorten hospital or residential care, or may serve as a transition from inpatient to outpatient care. For others, PHPs may help avoid the need for full hospitalization. PHPs for eating disorders generally include 4–7 days of treatment with two or three supervised meals each treatment day.

Residential Treatment Centers

RTCs offer specialized treatment delivered in a full-time setting. Treatment for individuals with eating disorders includes support for all meals and snacks, in addition to other treatment components. RTCs are considered appropriate for individuals who need significant supervision, but whose medical and psychological status does not require hospital-based care. RTCs treat individuals who are voluntary participants in their treatments. In the United States, most states require that RTC units remain unlocked, and although residents may be expected to stay for comprehensive treatment, RTCs generally allow residents to leave at any time. Treatments delivered within an RTC may include similar goals to those of an inpatient program. Third-party payer limitations may influence the setting in which a particular individual may receive 24-hour care available 7 days per week.

Inpatient Program

Psychiatric hospitalization is the highest (i.e., most intensive) level of care and may be necessary for some individuals with eating disorders, especially underweight individuals with AN. In contrast to the other levels of care previously described, specialized inpatient programs

include significant input from medical personnel, including psychiatrists. Hospital settings are used for individuals with eating disorders who require 24-hour attention for medical, psychiatric, and behavioral disturbances associated with their illnesses. Most patients with BN and BED do not require hospitalization and receive intensive treatment in less intensive settings; however, severe concurrent medical or psychiatric problems or poor response to previous outpatient treatment may be indications for inpatient treatment.

Summary

Intensive treatment may be delivered across a range of treatment settings. The treatment utilizes several modalities and is generally delivered by mental health clinicians from various disciplines. Most intensive treatment programs use group therapy and supervised meals as core elements. Pretreatment evaluation is important for selecting the appropriate level of care. Clinical severity, prior treatment experience, financial/third-party payer status, and geographical limitations are all considerations in selecting an appropriate treatment setting.

Studies of Intensive Treatment for Eating Disorders

Despite widespread use of intensive treatment for eating disorders, particularly AN, few randomized controlled trials have investigated their efficacy, and very little data have been published about the specific components of care included in these treatments. However, a larger body of evidence from longitudinal studies and case series indicates that intensive treatment for eating disorders can be effective in both the immediate stabilization and long-term management of both AN and BN.

In a randomized controlled trial focusing on the immediate efficacy of intensive treatment for eating disorders, Kong (2005) compared modified day treatment and traditional outpatient treatment in a group of 43 patients with an eating disorder diagnosis, 16 of whom had AN. Results indicated that patients in the day treatment group had significantly higher increases in body mass index (BMI) and decreases in binge-purge behavior and eating disorder symptomatology at the end of approximately 10 weeks of treatment than patients in the outpatient group, although the results were not stratified by diagnosis. Williamson et al. (2001) assigned patients with AN and BN to either inpatient hospitalization or a PHP based on severity criteria, including body weight, presence of medical complication, and history of treatment failure. The authors described significant improvement in BMI for patients with AN from baseline (mean BMI=17.52 kg/m^2, SD=1.95) to the end of treatment (mean BMI=19.32 kg/m^2, SD=1.69), as well as significant decreases in symptoms, with no impact of specific treatment type. In both treatment settings, patients with BN demonstrated improvement in depression scores, binge eating, restrictive eating, fear of fatness, purging behavior, and avoidance of forbidden foods (Williamson et al. 2001). Taken together, the data suggest that an intensive approach may be more effective than traditional outpatient care at increasing weight and decreasing eating disorder symptoms by the end of the treatment course, and that although both inpatient and day treatment programs may help to restore weight, inpatient treatment may do so faster.

In addition to these comparative studies, there are many accounts of inpatient programs for AN patients (Brewerton and Costin 2011b; Collin et al. 2010; Delinsky et al. 2010; Gentile et al. 2008; Treat et al. 2005) and day treatment or partial hospitalization programs for patients with AN and BN (Exterkate et al. 2009; Olmsted et al. 2003; Schaffner and Buchanan 2008; Willinge et al. 2010) that report significant increases in weight and BMI, decreases in binge-purge or restrictive behavior, and better psychological functioning at the conclusion of treatment.

Interpreting or generalizing from studies of intensive treatment is challenging because individuals who are referred to or select higher-intensity treatments for eating disorders may be differently affected by their illnesses; therefore, it is important to consider the characteristics of the patient population who receive a higher level of care. In a prospective naturalistic follow-up study of 246 patients with AN or BN (Keel et al. 2002), having a diagnosis of AN was associated with receiving more inpatient treatment, and more severe psychiatric pathology predicted greater utilization of care, leading the authors to postulate that this higher proportion of severely ill patients in intensive treatment settings may obscure treatment efficacy outside of randomized controlled treatment outcome studies. Similarly, predictors of future inpatient admission in 148 adolescents with AN (Gowers et al. 2010) included lower baseline percent weight for height and the presence of mood symptoms, whereas lower percent weight for height and higher AN symptom burden predicted more admissions over time and shorter time to first admission. These findings support the intuitive notion that sicker patients are more likely to receive inpatient or other intensive treatment, and align with the American Psychiatric Association's (2006) practice guideline for inpatient admission, which recommends that low-weight patients (e.g., with body weights <85% of ideal) are appropriate for the highly structured programs.

Although appropriate patients may benefit from completion of intensive treatment, many patients leave inpatient settings before finishing the course of treatment or before reaching their target weight. A review of 26 studies (Fassino et al. 2009) found that dropout rates from inpatient eating disorder programs for patients with AN, BN, and eating disorder not otherwise specified (EDNOS) ranged from 20.2% to 51%. The most consistent predictor of treatment dropout across studies was the diagnosis of the binge-purge subtype of AN, but many other factors, including impulsivity, fear of maturity, low self-directedness, low cooperativeness, weight on admission, eating disorder symptom burden, and greater psychiatric difficulty overall, were found to be related to early termination from inpatient treatment (Fassino et al. 2009; Wallier et al. 2009). More recently, a large-scale study of 601 inpatients with AN (Huas et al. 2011) found dropout rates of 50%–56%, with predictive factors of dropout including having at least one child, low desired BMI, low minimum BMI, paranoid ideation, high levels of eating behavior symptoms, and low levels of education. Dropout rates from day hospital or partial hospital treatment have been less commonly reported, but available data suggest lower rates than those seen in inpatient treatment, ranging from 13.5% to 18.8% (Franzen et al. 2004; Olmsted et al. 2003).

For patients who are able to complete intensive treatment, studies demonstrate positive and sustained change over time. A large study of 472 adult inpatients with AN or BN (Lowe et al. 2003) found sus-

tained increases in BMI and decreases in depressive and eating disorder symptoms 3 months following program discharge, although only 35% of the individuals with AN and 27% of those with BN completed the follow-up assessments. Other cohort studies that followed adults with AN who had completed inpatient treatment and demonstrated weight restoration or symptom improvement on discharge also found longer-lasting benefit. Gentile et al. (2008) described a sample that maintained a healthy BMI at 17 months following hospital discharge, and Bowers and Ansher (2008) found sustained improvements in self-reported symptoms 1 year following hospitalization, although their findings were limited because only half of the original sample completed follow-up assessments. Bean et al. (2004) reported an average weight gain among adult patients with AN of 9 pounds at 15 months following completion of residential treatment.

Other data suggest that the long-term outcome of intensive treatment compared with outpatient treatment may be less clear. In a randomized controlled trial, 90 young adults were assigned to receive inpatient treatment, outpatient individual and family psychotherapy, outpatient group therapy, or a no further treatment group that was referred to a family doctor or local consultant (Crisp et al. 1991). At 1-year follow-up, weight change in all groups was significant, but across groups only weight gain in patients who received outpatient treatment was significantly more than that in the no treatment group.

Data suggest that inpatient treatment may create sustained change even among patients with severe disease as indicated by very low BMI on admission (Gentile et al. 2008) or long-standing history of AN (Rø et al. 2004). In the Rø et al. study, improvements in eating disorder and psychiatric symptoms were maintained by 42% of patients at 1-year follow-up, although 58% had a poor outcome. There are also data for sustained efficacy of day treatment for patients with AN and BN, with improvements in BMI and binge frequency at discharge maintained and many cognitive and psychological measures improved at 3-month follow-up (Willinge et al. 2010) and maintenance of discharge BMI and improvement in eating behavior after a mean of 17 months postdischarge (Gerlinghoff et al. 1998), although the latter study reported a 61% retention rate.

Although most studies focus on adult or mixed adolescent and adult populations, data for strictly adolescent populations are somewhat mixed. In a randomized controlled trial of 167 adolescents with AN assigned to psychiatric inpatient treatment (with experience in treating eating disorders), specialized outpatient eating disorder treatment, or psychiatric treatment as usual in the community, all groups demonstrated improvement in weight with no statistical differences among treatment settings (Gowers et al. 2010). A 1-year follow-up study of 57 adolescents with AN whose weight had been restored and who showed modest symptom improvement at discharge from inpatient treatment found that 28.1% had good outcomes (defined as weight within 15% of average weight range and regular menstruation), whereas 59.6% had poor outcomes (defined as weight below 85% of average, absent or near-absent menstruation, or signs and symptoms of BN) (Salbach-Andrae et al. 2009). In a 6-month follow-up study of 26 adolescents with AN or EDNOS following completion of a day treatment program, Goldstein et al. (2011) found significant increases in BMI from posttreatment and significant improvements in many eating disorder symptoms. These data suggest that ado-

lescents may benefit more from day treatment than inpatient treatment.

Finally, it is important to consider evidence for the risk of relapse or return of eating disorder behavior or low weight following initial recovery. The estimated risk varies depending on the definition of relapse and the duration of follow-up, but several studies following patients with AN for 1–15 years after discharge from inpatient treatment programs have found relapse rates between approximately 30% and 41% (Carter et al. 2012; Eckert et al. 1995; Strober et al. 1997). Of note, the highest risk of relapse appears to be within the first year following discharge from hospitalization, with one study (Carter et al. 2012) narrowing the window of highest relapse risk to 4–9 months posttreatment. Many possible predictors of relapse have been examined but only a few identified, including low percentage of body fat (Bodell and Mayer 2011), diet composition (Schebendach et al. 2008), binge-purge subtype of AN, severity of checking behaviors before treatment, low levels of motivation during and after treatment (Carter et al. 2012), and compulsive drive to exercise upon discharge (Strober et al. 1997). One study (Castro et al. 2004) found a readmission rate of 25% within 1 year following hospital discharge among individuals who had achieved full weight recovery during inpatient treatment; predictors of readmission included young age and low rate of weight gain during initial hospital stay.

Some studies have addressed the long-term course (e.g., 5 or more years) of AN following intensive treatment, although it is difficult to link outcomes to the index treatment due to the naturalistic nature of the studies and the high likelihood of intervening treatments during the follow-up period. However, possible predictors of poor outcomes within 5–15 years of intensive treatment include earlier relapse following discharge (Strober et al. 1997), sexual problems (including issues with body contact, sexual feeling, and arousal), impulsivity, long duration of inpatient treatment, chronicity of symptoms (Fichter et al. 2006), later onset of disease, low minimum BMI (Tanaka et al. 2001), purging symptoms, advanced age at presentation, and high social status (Deter and Herzog 1994). Across many studies of AN, a major factor associated with outcome following discharge from intensive treatment relates to discharge weight. Two studies (Kaplan et al. 2009; Lock and Litt 2003) found that the only factor predicting good outcome, generally defined as weight maintenance, at 1 year following inpatient treatment is the BMI, including discharge weight and weight loss in the first 28 days following discharge, whereas another study (Lund et al. 2009) found that only the rate of weight gain during inpatient treatment predicted positive outcome at 1 year, with a threshold for significance of greater than 0.8 kg gained per week. Several other studies also include rate of weight gain and/or discharge BMI among the factors associated with outcome (e.g., Castro et al. 2004; Howard et al. 1999).

Longer hospitalization is associated with greater degree of change in BMI (Collin et al. 2010). As the average length of hospitalization for eating disorders decreased in the 1980s and 1990s, the average discharge BMI decreased and the readmission rate increased (Wiseman et al. 2001). A 10-year follow-up study of patients who had completed >30 days of residential treatment found that the best predictor of recovery in AN patients was discharge BMI (Brewerton and Costin 2011a), indicating the importance of weight gain for both short- and long-term outcomes.

In summary, there is evidence that supports short- and long-term benefits of in-

tensive treatment for weight restoration and improvement of eating disordered symptoms, although dropout rates are high. Higher discharge weights have been associated with improved outcome.

Determining Level of Care

A patient's weight, rate of weight loss, cardiac function metabolic status, behaviors, psychiatric comorbidities, and social circumstances should be considered when determining the most appropriate treatment setting that will allow the patient to reach treatment goals. Goals might include healthy weight restoration, reduction or elimination of bingeing and purging, treatment of medical complications, enhanced motivation to reestablish healthy eating patterns, education about nutrition, help in assessing and changing dysfunctional cognitions related to the eating disorder, treatment of associated psychiatric symptoms, enlistment of family support, and relapse prevention (American Psychiatric Association 2006).

Clinical Challenges

Several clinical challenges are commonly encountered in the delivery of intensive treatment for eating disorders. Patients' ambivalence regarding treatment goals, and relatedly, the treatment interventions targeting persistent disordered eating behaviors, including restriction of dietary intake and postmeal purging, may be difficult for staff to negotiate. Therapeutic sessions should include discussion of motivations for behavioral change, with particular focus on the factors that contributed to the decision to seek treatment. Clinical programs generally have policies and procedures to help patients resist engaging in behaviors of illness. For example, supervision during and following meals aims to support and redirect patients around urges to engage in symptoms. Peer supervision and frank clinical discussions with all team members may be helpful to maintain consistency and avoid undue rigidity around clinical management decisions.

Establishing clear treatment expectations may help manage some challenges related to ambivalence and difficult behavioral changes. For example, at Columbia University's eating disorders program at the New York State Psychiatric Institute, patients receive substantial information about unit expectations and unit policies prior to admission and are asked to confirm their willingness to participate in the described program during a screening interview. Specifically, the preadmission screening asks potential patients to consider whether they are willing to consume 100% of prescribed foods and supplements and, if diagnosed with AN, to fully normalize weight. During screening, candidates are informed that the unit is seeking individuals who are likely to make the best use of its clinical resources.

Patients with particularly limited insight into their illness may require involuntary commitment for some or all of their eating disorder treatment. Physician-certified or court-ordered treatment poses challenges both for patients and for specialized staff. Staff may find it useful to consider the medical urgency of the clinical presentation and the life-sustaining elements of the treatment in their treatment planning. Sometimes, patients describe a sense of relief or acceptance that accompanies intensive treatment because of the perception that they "have to" eat or "have no choice" about the treatment components. Furthermore, a study

of hospitalized patients with eating disorders found at 2-week follow-up that 41% of patients with AN and 50% of patients with BN who did not endorse need for hospitalization at the time of admission came to believe they did need admission (Guarda et al. 2007). The challenge to staff includes helping patients connect with their motivations for improvement, however limited they may be.

Intensive treatment for eating disorders is a potentially effective intervention for individuals who are struggling with weight and disordered eating behaviors, such as binge eating and purging, and who need more structured treatment than what traditional outpatient interventions provide. For medically compromised patients with AN, intensive treatment can be life saving. Offered across a range of settings, intensive treatment is an effective way to manage the serious psychiatric and medical features that may be associated with AN, BN, or BED.

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CHAPTER 33

Primary Care and Consultation-Liaison Interventions for Somatic Symptom and Related Disorders

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In any given week, most individuals experience one or more somatic symptoms, and many of those who are symptomatic seek medical care. Moreover, up to 50% of primary care patients present with symptoms that cannot be explained by a general medical condition, and roughly 10% of all medical services are provided to individuals for whom evidence of organic pathology is not apparent (Greenberg et al. 2008). Individuals who somatize (i.e., experience and attribute medically unexplained physical symptoms to an organic cause and seek medical help for it) are underrecognized by physicians. Their care often involves unwarranted costs that strain limited medical resources, and they are at risk for iatrogenic harm when unnecessary diagnostic procedures, misdirected drug trials, and unnecessary surgeries are performed. When symptoms are so severe that significant distress and impairment in occupational and social functioning develop, the individual should be assessed for a somatic symptom disorder. In this chapter, we review the workup and treatment of three types of somatic symptom disorders: somatic symptom disorder, conversion disorder, and factitious disorder.

Terminology

According to DSM-5 (American Psychiatric Association 2013), the key features of *somatic symptom disorder* involve disproportionate and excessive thoughts, feelings, and behaviors associated with somatic concerns. If an individual lacks somatic symptoms yet still has persistent disproportionate thoughts, feelings, behaviors, and preoccupations that he or she might be sick, that person should be assessed for *illness anxiety disorder.* It is important to note that one can have a somatic symptom disorder whether or not the symptoms have a medical explanation.

Conversion disorder involves the loss or change in sensory or motor function that is suggestive of a physical disorder but whose findings provide inconsistent or incompatible evidence with a known neurological or medical condition.

Factitious disorder is a related disorder that should be considered and excluded before making the diagnosis of conversion disorder. Factitious disorder involves the conscious or intentional production of somatic or psychiatric symptoms (e.g., delusions), although the underlying motivation may be unconscious (see Table 33–1 for the differences between conversion disorder, factitious disorder, and malingering [which is not considered a mental disorder but is often confused with factitious disorder]). Factitious illness emerges from a desire to achieve the social status of a sick person (with its traditional benefits [e.g., protection, blamelessness, attention, support, release from work]). The individual with factitious disorder attempts to capture the attention of others who are empowered to convey certain privileges and considerations to the person who appears sick. The sick role is attained by faking symptoms, fabricating histories, or manipulating one's body to appear as though one has a serious condition requiring medical or surgical care. The medical arena (represented by multiple disciplines) then supplies support and sympathy. Importantly, the goal of appearing ill is not to receive secondary gain, as in malingering; rather, the person with factitious illness aims to achieve the sick role. The attention of others (i.e., the reward) then serves to sustain their hoax.

Presenting Features of Factitious Disorders for Medical Attention

Factitious disorders manifest in myriad ways depending on the meaning of illness; almost any somatic or psychological symptom or condition can be simulated, feigned, or created. Manifestations may morph over time and be shaped by the responses of evaluators. Individuals with these disorders are typically seen by nonpsychiatric physicians, who are often faced with incongruent findings on physical examination and unexplainable laboratory results. The hoax being perpetrated can usually be detected with appropriate testing (e.g., seizures without an abnormal electroencephalogram pattern, neurological signs that do not conform to anatomical pathways). Unfortunately, patients can obfuscate the diagnosis by building on their medical knowledge and creating more compelling phenomenology that resembles real disease states. Table 33–2 includes a listing of the signs and symptoms of some selected disorders and the methods often used to determine whether a patient has a real or factitious disorder.

TABLE 33–1. Differences in motivation and behavior for conversion disorder, factitious disorder, and malingering

Disorder	Primary diagnostic feature	Motivation (gain produced)	Behavior (of symptom production)
Conversion disorder	Motor or sensory function symptom(s) or deficit(s) inconsistent with recognized conditions	Unconscious	Unconscious
Factitious disorder	Intentional production of medical or psychological symptoms to assume the role of a sick patient	Unconscious	Conscious
Malingering	Intentional production of symptoms to obtain some external gain	Conscious	Conscious

Diagnosis of Somatic Symptom and Related Disorders

Although diagnosing somatic symptom disorder is straightforward if the DSM-5 criteria are followed, diagnosing factitious disorder and conversion disorder is more challenging (unless direct evidence is found). Evaluation involves taking a full history, completing a physical examination, and obtaining as much information as possible about the patient (e.g., gathering data from prior health care providers, family, and friends, if the patient allows). Use of a systematic approach, taking into consideration each of the pertinent medical and psychiatric diagnoses, will decrease the chance of overlooking a condition with a primarily physiological source. The diagnosis should remain provisional until there is considerable evidence to the contrary. Patients with these disorders can develop the disorder after having gained attention from having had a true medical illness. Thus, it is especially important to consider conditions that affect multiple organ systems or produce variable presentations (e.g., multiple sclerosis, acute intermittent porphyria, HIV infection, scleroderma, rheumatoid arthritis, systemic lupus erythematosus). Likewise, it is important to consider whether multiple psychiatric disorders (e.g., mood, anxiety, personality, substance-related disorders) are present and to consider whether the presentation is better accounted for by one or another. Tests such as the Minnesota Multiphasic Personality Inventory (MMPI; Butcher et al. 2001) and full neuropsychological test batteries can also help to refine the diagnosis.

Laboratory studies can clarify the diagnosis in some cases. (For example, presence of C-peptides can reveal an exogenous source of insulin, whereas detection

TABLE 33–2. Selected conditions simulated in factitious illness: signs, symptoms, and treatment

Signs, symptoms, or diseases simulated or caused by factitious behavior	Comments on patient's medical presentation, strategy, or desire	Workup and diagnosis of the fabrication
Anemia	Self-inflicted bleeding	Assess for an induced site of blood loss, venipuncture, or instrumentation (especially of orifices).
Anticoagulation problems	Surreptitious anticoagulation abuse	Confirm that patient does not need warfarin, administer vitamin K; recheck prothrombin time/international normalized ratio.
Aplastic anemia	Ingesting alkylating agents (such as chemotherapy agents)	Assay for suspected drug.
Arrhythmia	Surreptitious laxative use, thyroxine abuse, digitalis, β-blockers, calcium channel blockers	Request telemetry with supervised lead placement to avoid manipulation. Measure serum levels of suspected medications.
Bacteremia	Exogenous material in the blood (most commonly stool or pet flora)	Suspect when polymicrobial bacteria or unusual organisms are obtained in blood cultures.
Cancer	Manipulation of medical records or providing false family history (e.g., in an attempt to obtain prophylactic mastectomy)	Contact the authors of medical records.
Chronic diarrhea	Surreptitious addition of water to stools; laxative use by patients	Request urine and stool laxative screens. Measure fecal fluid osmolality. Test stool for phenolphthalein to evaluate for laxative abuse.

TABLE 33–2. Selected conditions simulated in factitious illness: signs, symptoms, and treatment *(continued)*

Signs, symptoms, or diseases simulated or caused by factitious behavior	Comments on patient's medical presentation, strategy, or desire	Workup and diagnosis of the fabrication
Cushing's syndrome	Surreptitious addition of exogenous glucocorticoids	Measure upstream metabolites to check for evidence of suppressed pituitary secretion of adrenocorticotropic hormone; check cortisol and corticosterone as both are co-secreted (corticosterone will not be elevated if cortisol is surreptitiously added to urine samples).
Fever of unknown origin	Ingestion of hot beverage or placement of warm wax in ears	Observe patient during temperature measurement using electronic thermometer; assess for other signs of fever.
Hematuria	Tampering with urine samples to produce false-positive tests	Observe urine collection. Perform three-tube test to rule out urethral trauma.
Hemiplegia	Weakness, but typically without atrophy	True weakness is smooth, not jerky or catching. Test "hand over head" (hold arm vertically over supine patient, braced at elbow so that releasing hand will, by gravity, hit the face and patient will avoid it). Test Hoover's sign by cupping hands under supine patient's heels, asking patient to raise good leg, and feeling downward pressure of "plegic" leg.
Hyperaldosteronism	Ingestion of black licorice (glycyrrhizic acid can lead to treatment-resistant hypokalemia, metabolic alkalosis, and hypernatremia)	Request serum assay for glycyrrhizic acid.

TABLE 33–2. Selected conditions simulated in factitious illness: signs, symptoms, and treatment *(continued)*

Signs, symptoms, or diseases simulated or caused by factitious behavior	Comments on patient's medical presentation, strategy, or desire	Workup and diagnosis of the fabrication
Hypertension	Use of valsalva maneuver	Request serum or urine assay for pseudoephedrine. Ensure no use of valsalva maneuver during blood pressure measurement.
Hypoglycemia	Manipulation of testing strips, exogenous use of insulin	Measure serum insulin, C-peptide (high C-peptide indicates endogenous insulin, although it can also be elevated in renal failure); assays for metformin.
Hypotension	Abuse of antihypertensive agents	Request serum assay for β-blockers or calcium channel blockers.
Intestinal pseudo-obstruction	Ingestion of motility slowing agent or loperamide	Measure loperamide or other agents in blood or stool.
Nausea/vomiting	Excess ipecac consumption	Look for low serum potassium and chloride. Ipecac toxicity can be associated with elevated creatine phosphokinase, leukocytosis, or transaminitis. Measure serum or urine emetine levels to detect ipecac consumption.
Nephrolithiasis	Submitting nonphysiological renal stones; or subcutaneously implanting metal in abdomen to mimic stone on plain film	Request microscopic examination, infrared spectrophotometry, crystallography, or X-ray diffraction to characterize suspected nonphysiological crystals.

TABLE 33–2. Selected conditions simulated in factitious illness: signs, symptoms, and treatment *(continued)*

Signs, symptoms, or diseases simulated or caused by factitious behavior	Comments on patient's medical presentation, strategy, or desire	Workup and diagnosis of the fabrication
Pheochromocytoma	Self-administration of epinephrine or isoproterenol, or use of valsalva maneuver	Measure serum chromogranin A to identify true pheochromocytoma. Measure vanillylmandelic acid, which is also used and can be elevated due to foods high in vanillin.
Respiratory failure	Desire to be intubated	Look for incongruities in arterial blood gas measurements.
Wounds	Introduction of human/animal feces, toxins, aquarium water, or foreign bodies into wounds	Apply fluorescein or tetracycline to wound, then examine hands and nails for fluorescence. Nonhealing wounds will heal when casted.

Source. Adapted from Kenedi C, Shirey K, Hoffa M, et al: "Laboratory Diagnosis of Factitious Disorder: A Systematic Review of Tools Useful in the Diagnosis of Munchausen's Syndrome." *New Zealand Medical Journal* 124(1342):66–81, 2011.

of exogenously administered thyroid hormone, epinephrine, anticoagulants, or vanilla extract may establish the surreptitious use of medications.) Notably, every test has less-than-perfect sensitivities and specificities, as well as false positives and false negatives. Collateral informants may be crucial when confirming the diagnosis. If the patient is hospitalized, a search of the room and belongings (for vials of insulin or other medication, syringes, or objects that could be used to create wounds) can aid in making the diagnosis (being mindful of the patient's right to privacy). Observation of the patient, via a one-to-one observer, can provide further evidence of self-injury.

Treatment of Somatic Symptom and Related Disorders

Treatment of somatic symptom and related disorders requires building a therapeutic doctor-patient relationship in which the patient's distress is accepted as real. Once this relationship is established, several factors—assigning a treatment team to develop a treatment plan, informing the patient of the diagnosis and treatment plan, promoting positive reinforcement, considering and treating potential comorbid conditions, and referring pa-

tients to psychiatric specialists—all play important roles in the treatment process.

Assigning a Treatment Team to Develop a Treatment Plan

The first step in management is the assignment of one physician as a leader of a multidisciplinary team (including physicians, consultants, nurses, social workers, hospital administrators, hospital ethics staff, attorneys, and risk managers). This person should oversee the ordering of all tests and consultations, as well as the reviewing of the results. In most cases, this person will be the outpatient primary care physician. Even though team members may have opinions that vary, all involved should ultimately agree on the diagnosis. To encourage collaboration, the leader can have all specialists on the case submit their recommendations for diagnostic testing (with the understanding that if a test comes back negative, the workup will be considered complete and the patient will be informed). Clear and consistent communication between physicians and consultants regarding the treatment plan is essential to minimize staff splitting and to facilitate agreement about what the patient should be told regarding the need for further workup.

Informing the Patient About the Diagnosis and Treatment Plan

The next step in treatment involves informing the patient about the diagnosis and recommended treatment; this requires a therapeutic alliance with the patient. Some patients will be angry, defensive, and flee from treatment, whereas others will be grateful that a diagnosis has been established. Regardless of whether or not a physician uses the actual diagnostic label, patients can benefit from understanding how their condition affects their life and realizing that their distress can be addressed.

Explaining to the patient that he or she may be more attuned to benign visceral and somatic sensations can be beneficial. In the case of conversion symptoms, one can reassure the individual—that is, by explaining that the symptom(s) will ultimately improve, despite a gradual recovery—while providing reassurance that the body parts in question appear normal. Symptoms may diminish if the patient does not need to admit to the behavior (e.g., when told that the symptom will resolve with physical therapy, medications, or other treatment modalities). The lack of a life-threatening disease should be seen as "good news" rather than as a cause for further frustration. Another strategy, particularly when symptoms persist, is to redirect attention from the symptoms to the role that stress and its exacerbation has on the condition. The patient's psychological strengths and the absence of other psychopathology are more important for the outcome than is the actual conversion symptom. In the case of the hospitalized patient who fails to improve with suggestions, symptoms may improve after the individual is told that he or she may need to be transferred to a psychiatric unit.

Promoting Positive Reinforcement and Avoiding Negative Reinforcement

Physicians should avoid reinforcing maladaptive behaviors (e.g., by validating the belief that the patient is in fact ill).

Sometimes this happens unintentionally through direct questioning while taking a detailed history, and doing so may contribute to the evolution of new complaints. Refusing to reinforce the behavior while simultaneously avoiding alienation of the patient can be difficult.

Conducting a follow-up visit is probably more important than is any prescribed treatment. Regular, brief visits that are not contingent on symptoms should be scheduled, every 1–2 weeks (and gradually reduced to every 4–6 weeks, as tolerated), to assuage the patient's perceived need to have symptoms that maintain the relationship with a physician. If the patient calls between scheduled visits, the physician can return to more frequent visits. The patient needs to learn that seeing a physician is not contingent on having symptoms. Early in the visit, particular attention should be paid to setting goals for each appointment, with a particular focus placed on the patient's emotional concerns. A physical examination should be performed at each visit, at which time the physician can inquire (in a supportive manner) about the areas of stress in the patient's life, without inference to stress as a cause for the increase in somatic concerns. Patients will ultimately come to reveal personal concerns after trust is built. If the patient provides permission, family members can be contacted. Learning about patient and family strengths can be a useful focus, as can inquiring about how life would be different if the patient were free of symptoms.

When new symptoms develop, the physician should conduct a focused physical examination and order procedures and treatments on the basis of objective evidence rather than on subjective symptoms. If the workup is unrevealing, the new symptoms should be added to the list of symptoms already attributed to the disorder.

Physicians should also consider teaching patients how to manage life stress rather than putting important activities on hold until their chronic somatic symptoms are resolved. Not attending work can reinforce illness behavior. Vocational counselors can assist patients who are not chronically disabled by their condition to find less stressful jobs that can help provide meaning and structure.

Ruling Out and Treating Comorbid Conditions

Persons diagnosed with somatic symptom disorder, conversion disorder, and factitious disorder are not immune to the development of other illnesses; therefore, they should be monitored for the development of new illnesses. In addition, other psychiatric disorders (e.g., depressive disorders, anxiety disorders, substance abuse disorders, personality disorders) are commonly associated with somatic symptoms. Sometimes the somatic symptoms improve as the other disorder improves; sometimes the somatic symptom disorder persists even after depressive disorder has been treated.

Referring Patients to Psychiatric Specialists

In working with patients who have somatic symptom disorders, the psychiatrist usually serves as a consultant who can clarify the diagnosis, the workup, and the management of the patient (see Table 33–3). Unfortunately, most patients with abnormal illness behavior do not accept referrals to psychiatric consultants, and the majority of patients fail to appear for their appointments even when scheduled.

Patients with somatic symptom disorders induce intense affective reactions (leading to the dismissal of all complaints

TABLE 33–3. Role of the psychiatric consultant in treating somatic symptom disorders

Assure the completion of the medical evaluation.
Diagnose a disorder if present or conceptualize the problem in another useful way.
Send a consultation note to the consultee outlining the diagnostic formulation and management strategies (e.g., scheduling frequent brief appointments, performing focused physical examination at each visit, avoiding all unnecessary interventions [diagnostic and therapeutic]).
Help the consultee build a therapeutic doctor-patient relationship.
Assist in making meaning of the patient's experience through understanding how genetics, life events, and personality style all influence the production of normal and abnormal physiological states.
Facilitate awareness of countertransference.
Diagnose and treat comorbid disorders (e.g., mood and anxiety disorders).
Facilitate referral to cognitive-behavioral therapy for symptom control, if appropriate.

as factitious), behavioral responses, and cognitive challenges that distract a primary physician from making an accurate diagnosis. Whenever possible, early involvement of a psychiatrist can facilitate making a diagnosis, and thereby prevent iatrogenesis. Consultation notes sent to the primary care physician (that outline the disorder, workup, and management of patient concerns and demands) have been effective in reducing health care charges and harmful medical interventions without compromising the health and satisfaction of patients.

Moreover, psychiatrists can play a key role in helping other physicians deal with negative countertransference. The physicians' mindset (being caring, trusting, and eager to help) can be challenged when dealing with patients who deceive, lie, or eagerly undergo diagnostic and surgical procedures for no apparent reason. Such reactions, as when patients shame their physicians, can lead physicians to order unnecessary procedures, to dispense addictive or dangerous treatments, and to make errors of omission or commission. Psychiatric consultants can help facilitate awareness of countertransference and help prevent doctors from acting on hostile feelings. Psychiatrists can also help reduce primary care team members' distress by helping them continue to be intrigued by their patients rather than being frustrated by them.

Finally, psychiatric consultants can take an active role in the management of patients (e.g., by using supportive, empathic, and nonconfrontational psychotherapy). Encouraging patient participation can diffuse a patient's need to create symptoms of factitious illness, conversion, or somatic illness behavior. Emerging data suggest that cognitive-behavioral therapy (CBT), particularly in the primary care setting, can help to identify and restructure cognitive distortions, unrealistic dysfunctional beliefs, worry, and behaviors that drive these disorders (Abbass et al. 2009). When appropriate, referring the patient for CBT can be helpful.

Conclusion

The techniques, approaches, and discussions described in this chapter are intended to help the patient modify his or her belief system and behavior. Lasting changes in beliefs and behaviors develop over time and in response to positive reinforcement.

Further research is needed on screening instruments to enhance accurate diagnoses, effective treatments, and preventative interventions for patients who suffer from abnormal illness behaviors. Ultimately, a stepped-care treatment model that helps to determine (based on severity of illness behavior) what type of professional specialist and intervention is needed may provide more efficient care of patients with somatic symptom disorder.

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CHAPTER 34

Pharmacological Interventions for Psychosomatic Disorders

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One of medicine's great challenges is the management of psychosomatic symptoms. These include medically ambiguous somatic symptoms, nonspecific neurological deficits, and the emotional, cognitive, and behavioral response to these symptoms. Although psychotherapy and modifications to behavior and lifestyle play the major roles in alleviating these symptoms, pharmacological intervention can also be helpful. This chapter reviews what is known about pharmacological interventions for three psychosomatic processes: illness anxiety, somatization, and conversion.

Because of the considerable diagnostic changes in the DSM-5 somatoform section, now labeled "Somatic Symptom and Related Disorders" (American Psychiatric Association 2013), there is a paucity of research that directly addresses treatment for these newly defined conditions. However, a body of well-conducted research over the last two decades has contributed substantially to the understanding of how to treat the precursor disorders of DSM-5; this literature informs our current review and recommendations (Table 34–1). *Illness anxiety disorder* is a less inclusive version of the former hypochondriasis in that it excludes individuals with prominent somatic symptoms. *Somatic symptom disorder* is an amalgam of the previous somatization disorder, undifferentiated somatoform disorder, hypochondriasis (with prominent somatic symptoms), and pain disorder. The criteria refinements for *conversion disorder* do not diminish the relevance of treatment results based on DSM-IV criteria (American Psychiatric Association 1994).

Although psychological factors affecting other medical conditions and factitious disorders are now included in the

TABLE 34–1. Pharmacological treatment principles for psychosomatic disorders

- Start low, because lower doses may be effective and better tolerated.
- Increase to higher doses if needed, which may be better for obsessional anxiety.
- Clarify that response may not be fully achieved until 8–12 weeks.
- Consider the dual role of serotonin-norepinephrine reuptake inhibitors (SNRIs) as benefiting pain disorders (chronic pain, neuropathic pain) and psychiatric ones (generalized anxiety, depression).
- Educate patients that somatic pain is mediated through central neural circuits that pharmacological treatments modulate.

DSM-5 diagnostic class of somatic symptom and related disorders, negligible data exist for pharmacological interventions for these disorders outside of treating comorbid mood or anxiety disorders. Therefore, these disorders are not covered in this chapter.

Illness Anxiety

Illness anxiety is a feature common to the diagnoses of somatic symptom disorder and illness anxiety disorder, with the former disorder distinguished primarily by prominent somatic symptoms. Pharmacological treatments that help to reduce obsessions or severe fearful preoccupations would be expected to help patients with both disorders.

Among patients with hypochondriasis, case reports and small clinical case series using different serotonergic medications showed high (70%–89%) responder rates ("much or very much improved") for treatment completers who continued taking the medication for a recommended 8–12 weeks. These medication trials included fluoxetine (Fallon et al. 1991, 1996; Viswanathan and Paradis 1991), clomipramine (Stone 1993), citalopram (Fallon and Feinstein 2001), paroxetine (Oosterbaan et al. 2001), and fluvoxamine (Fallon et al. 2003). Other agents have shown promise as well, including the tricyclic antidepressant (TCA) imipramine, with both norepinephrine and serotonin (5-HT) reuptake blocking properties (Wesner and Noyes 1991); nefazodone, primarily acting through postsynaptic 5-HT_2 receptors (Kjernisted et al. 2002); and duloxetine, with dual serotonin-norepinephrine reuptake inhibition (Hirschfeld 2005; Politi 2007).

Controlled data on the use of medication among patients with hypochondriasis are limited. A double-blind, randomized, placebo-controlled study examined the use of fluoxetine (Fallon et al. 2008), starting at 20 mg/day and increasing every 2 weeks by 20 mg to a maximum of 80 mg/day. Fluoxetine was well tolerated; there were no significant differences in dropout rates between the active treatment and placebo groups. More importantly, the response rate was significantly higher in the fluoxetine group (Figure 34–1).

A randomized controlled trial (RCT) involving 112 patients with DSM-IV hypochondriasis showed that paroxetine and cognitive-behavioral therapy (CBT) are each helpful short-term treatment options (Greeven et al. 2007). Patients were randomly assigned to receive one of three treatments for 16 weeks: parox-

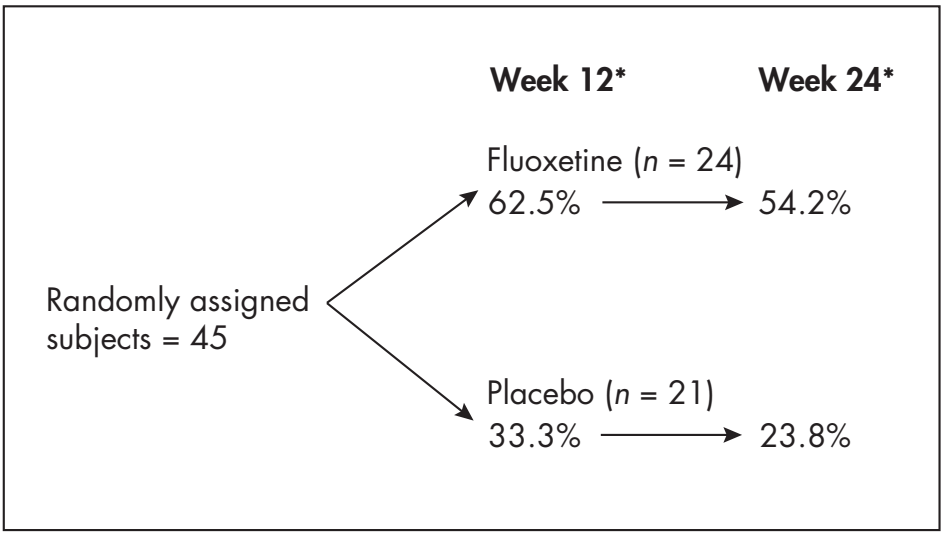

FIGURE 34–1. A controlled study of fluoxetine in treatment of hypochondriasis.
Intent-to-treat analysis using primary outcome of responder status (i.e., "very much" or "much improved" determination on Clinical Global Impressions Scale rated by independent evaluators).
*$P \leq 0.05$ for fluoxetine versus placebo.
Source. Data from Fallon et al. 2008.

etine, placebo (administered in a double-blind fashion), or CBT. Responders were defined as subjects who scored at least one standard deviation below the mean pretest score on the Whiteley Index. The responder rates for the intent-to-treat (ITT) and completer cohorts, respectively, were 45% and 54% for the CBT group, 30% and 38% for the paroxetine group, and 14% and 12% for the placebo group. For the ITT analysis, only CBT differed significantly from placebo, whereas in the completer analysis, paroxetine and CBT both differed significantly from placebo.

A prospective follow-up study by Schweitzer et al. (2011) of 58 patients with DSM-IV hypochondriasis who had participated in a trial of selective serotonin reuptake inhibitor (SSRI) treatment years earlier (mean=8.6, SD=4.5 years) showed that 60% of the patients no longer had a presentation that met DSM-IV criteria for hypochondriasis at long-term follow-up. In addition, there was an even higher remission rate among those individuals who reported using an SSRI during the follow-up interval than among those who reported that they had not (80% vs. 40%). This study suggests that a substantial proportion of patients with hypochondriasis who receive treatment with SSRIs achieve remission over the long term. Other factors contributing to long-term favorable outcome were a shorter duration of hypochondriasis prior to SSRI trial enrollment and not having reported a history of childhood physical abuse.

Somatization

Bothersome, unexplained somatic symptoms among patients in medical settings are common, yet systematic pharmaco-

logical studies of somatization are limited. In part, RCTs of somatization disorders were hindered prior to DSM-5 by the extremely narrow and highly restrictive criteria for diagnosis. Thus meta-analyses or studies that used more inclusive criteria for a spectrum of somatization disorders have been used to guide pharmacological treatment recommendations for patients with somatic concerns (Kroenke 2007; O'Malley et al. 1999; Sumathipala 2007).

A meta-analysis of 94 controlled trials (O'Malley et al. 1999) showed a considerable benefit (OR=3.4 [95% CI 2.6–4.5]) for the use of antidepressants, with TCAs showing greater efficacy than SSRIs, for a range of unexplained medical symptoms and functional syndromes. Interestingly, physical improvement typically did not correlate with depression response. This indicates that patients with somatoform disorders may benefit from these medications whether or not they have comorbid depression.

A meta-analysis by Kroenke (2007) reviewed a total of 34 RCTs involving 3,922 patients with DSM-IV somatoform disorders, including somatization disorder as well as the more inclusive categories of "abridged somatization" and medically unexplained symptoms. Although the meta-analysis showed clear evidence for CBT and for a consultation letter to the primary care physician in benefiting somatization disorder, only limited favorable evidence existed for improvement with antidepressant treatment compared to placebo. The treatments included St. John's wort (Müller et al. 2004), opipramol (a tricyclic anxiolytic with high affinity for sigma receptors not available in the United States) (Volz et al. 2000), and extended-release venlafaxine (although not statistically significant) (Kroenke et al. 2006). In addition, Muller et al. (2008), in a double-blind controlled trial among 51 patients with multisomatoform disorder, reported that at week 12, escitalopram (10–20 mg/day), compared with placebo, was associated with lower symptom scores, increased response and remission rates, and improved functioning.

A key issue for disorders with prominent somatization is the recognition that depressive, anxiety, and somatic symptoms commonly co-occur, and that treatment needs to address all symptoms. In a cohort study, Kroenke et al. (2011) followed for 12 months 500 patients in the Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP) study; these patients had persistent back, hip, or knee pain, with or without depression. The authors found that a change in either pain or depression severity was an equally strong predictor of subsequent severity of the other symptom. Thus, the study emphasized the need for recognition and management of both conditions simultaneously.

For management of comorbid pain and depressive symptoms, optimized antidepressant therapy using a serotonin-norepinephrine reuptake inhibitor (SNRI) combined with pain self-management therapy can be highly effective, with sustained response demonstrated in one study over a 12-month interval (Kroenke et al. 2009). In a randomized study of 112 patients with multisomatoform disorder, the improvement in somatic symptoms associated with SNRI use was predominantly restricted to those somatic symptoms associated with pain and not demonstrated in the somatic symptoms in which pain was not prominent (Kroenke et al. 2006). Thus, SNRIs (e.g., duloxetine, venlafaxine) or TCAs (e.g., desipramine) may be preferable for symptom relief when pain is a prominent feature (Marks et al. 2009). The hypothesized mechanism for this preferential effect relates to the fact that norepinephrine reuptake inhibi-

tion affects the descending inhibitory pain pathways.

Disorders associated with pain that are sometimes labeled as "functional," such as fibromyalgia or irritable bowel syndrome, are not categorized as somatic symptom disorders in DSM-5 unless there is an excessive emotional, cognitive, or behavioral response to the syndrome. Nevertheless, agents effective for multisomatoform disorders may also be helpful for these functional disorders. For example, RCT data indicate that duloxetine is effective for the treatment of pain, functional impairment, and quality of life associated with fibromyalgia with and without major depression, especially for women (Arnold et al. 2004, 2005, 2007). Other medications that have been reported in controlled studies to be helpful among patients with chronic pain syndromes, such as fibromyalgia or neuropathic pain, include the $\alpha_2\delta$ ligands, such as pregabalin and gabapentin.

Conversion Disorder

Pharmacological treatment for conversion disorders remains as elusive as the etiology of these fascinating disorders, with sparse controlled trial data to guide care. Starting in the 1960s, intravenous amobarbital (sodium amytal) was considered a mainstay for the rapid diagnosis and resolution of conversion symptoms based primarily on case series and reports. However, six of seven controlled studies failed to find a difference in treatment response between various doses of amobarbital and placebo (Kavirajan 1999). Subsequent anecdotal evidence has shown symptom improvement in patients with conversion symptoms with a range of medications such as anxiolytics, SSRIs, β-blockers, and neuroleptics (Allin et al. 2005; LaFrance and Barry 2005; LaFrance and Devinsky 2004; Marazziti and Dell'Osso 2005; Voon and Lang 2005), although controlled data are still needed.

The general current treatment strategy for conversion disorders is to treat comorbid psychiatric disorders and somatic symptoms. Among patients with nonepileptic seizures, clinicians should taper unnecessary and potentially harmful treatments that may have been initiated for presumed seizure activity, using caution not to iatrogenically induce withdrawal states or other complications. When non-epileptic and epileptic seizures coexist, maintenance of at least one antiepileptic medication may be prudent, especially if the mood-stabilization property of the medication is beneficial for the patient. Some preliminary evidence indicates that SSRI use in patients with epilepsy symptoms can reduce seizures (Cardamone et al. 2013) and may reduce non-epileptic seizures as well, according to a pilot RCT with sertraline (LaFrance et al. 2010).

Conclusion

The evidence-based pharmacological treatments described in this chapter are intended to bolster clinicians' ability to partner with patients to relieve symptoms, alleviate psychological distress, and improve functioning, even when the etiology of suffering is unclear in the context of current medical knowledge. Psychosomatic disorders are at the frontier of medical pathophysiology. The medical field's understanding of the origin, propagation, and treatment of these complex and distressing symptoms is evolving. The treatments described in this chapter provide hope for symptom reduction among patients with illness anxiety, multiple somatic symptoms, and conversion disorders.

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Useful Web Site

Comparing Cognitive Behavioral Therapy, Antidepressant Medication, and Combined Treatment in Individuals With Hypochondriasis: http://www.clinicaltrials.gov/ct2/show/NCT00339079?cond=%22Hypochondriasis%22andrank=1

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CHAPTER 35

Intensive Interventions for Somatic Symptom Disorders

Lawson Wulsin, M.D.

This chapter focuses on the more intensive treatments delivered by mental health specialists for patients with somatic symptom disorders, usually in mental health specialty settings. Interventions delivered in the primary care and hospital consultation settings are covered in Chapter 33 ("Primary Care and Consultation-Liaison Interventions for Somatic Symptom and Related Disorders"). Although pharmacotherapy is often central to intensive treatment by mental health specialists, pharmacological interventions are covered in Chapter 34 ("Pharmacological Interventions for Psychosomatic Disorders"), leaving for this chapter the remaining approaches to the management of somatic symptom disorders.

Relative to other topics in psychiatry, knowledge of the treatment of somatic symptom disorders based on clinical tradition and rigorous scientific evidence is limited by patient and clinician barriers. Patients with somatic symptom disorders tend to avoid psychiatrists and other mental health specialists, who generally see only those patients with the more severe disorders. Primary care clinicians tend to avoid studying patients with somatic symptom disorders. Reviews of randomized controlled trials (RCTs) of somatic symptom disorders (Kroenke 2007; Sumathipala 2007) suggest that about 40 trials have been published over the past 40 years, most of them in specialty settings over short terms using a variety of interventions (medications, therapy, consultation letters, exercise, hypnosis, and combinations of treatments) on a variety of disorder definitions (medically unexplained symptoms, somatization disorder, hypochondriasis, conversion disorder, body dysmorphic disorder, and somatic symptom disorder, to name just the more common targets of treatment

studies). Compared with the literature on the treatment of depression, anxiety, or schizophrenia, for example, this is a small and heterogeneous group of studies that, nonetheless, point to some sound conclusions about effective treatments for somatic symptom disorders.

This discussion of the state of the art of treating somatic symptom disorders proceeds with several other limitations in mind. Most of the studies informing the current approaches come from Europe and North America. Relatively little scientific literature discusses the intensive treatment of somatic symptom disorders in Africa, Asia, Australia, or South America. Only five studies (Allen et al. 2006; Dickinson et al. 2003; Schilte et al. 2001; Smith et al. 1986, 1995) followed patients for longer than 1 year, so not much is known about the duration of treatment response over the extended course of these mostly chronic conditions.

Terminology

Although this chapter uses terms consistent with DSM-5 terminology (American Psychiatric Association 2013), for historical continuity it helps to understand the overlap with DSM-IV terminology (American Psychiatric Association 1994) and with synonyms commonly used around the world. In DSM-IV this collection of disorders fell under the umbrella of *somatoform disorders,* a term that never gained traction outside of psychiatry and was not popular within psychiatry. Synonyms that have appeared in the literature and are more common in Europe include *functional somatic syndromes* and *multisomatic symptom disorders.* These terms sometimes imply the inclusion of disorders that did not fall under the DSM-IV somatoform disorder umbrella, such as chronic fatigue syndrome and irritable bowel syndrome. A newer term, *bodily distress disorders,* is under consideration as a category of disorders for the next edition of the World Health Organization's *International Classification of Diseases* (ICD-11), scheduled for release in 2015. These multiple disorder names and shifting boundaries around the scope of the terms reflect the field's insufficient understanding of the nature of these disorders and their treatments.

General Principles of Intensive Treatment

The most recent succinct summary of the recommended approach to somatic symptom disorders comes from the Netherlands Institute for Mental Health and Addiction and the Dutch Institute of Healthcare Improvement (van der Feltz-Cornelis et al. 2012). This multidisciplinary guideline for the management of medically unexplained physical symptoms (MUPS) and somatic symptom disorder (SD) "aims at setting a standard for providing evidence-based diagnosis and treatment to patients with MUPS and SD" (p. 168). The guideline authors argue for a common approach across somatic symptom disorders, including cognitive-behavioral therapy (CBT), treatment of comorbid depression and anxiety, psychiatric consultation letters to the relevant primary care clinicians, and stepped care guided by patient risk profiles. Mental health specialists are recommended for moderate- and high-risk patients, particularly those with long-standing somatic symptom disorders and a perturbed doctor-patient relationship with their primary care clinician. Mental health inpatient multidisciplinary treatment is recommended for severe cases.

With the exception of conversion disorder (also called "functional neurological symptom disorder"), which is usually an acute condition with symptoms that resolve within days to weeks, most somatic symptom disorders persist chronically over many months or years. The first step in managing somatic symptom disorders with a prolonged course is to aim for care rather than cure (Sharpe et al. 1992; Smith et al. 2000). This step requires setting achievable short-term goals as well as modest long-term goals. These negotiations can be difficult because they demand challenging some illness beliefs and reformulating the illness in terms that lend themselves to a variety of treatments. Tailoring treatment plans to the individual patient's symptom profile, illness beliefs, and dominant mood states lays the foundation for effective treatment planning.

Given that no single treatment has proven more effective than another treatment for a single subtype of somatic symptom disorders, some experts have proposed that the selection and intensity of the intervention should be driven more by the severity or complexity of the disorder than by its subtype (Schröder 2010; Schröder et al. 2012). Schröder and others have proposed a stepped care model for the management of functional somatic syndromes. At levels 1 and 2, the primary care clinician uses a combination of watchful waiting and structured counseling. At level 3, moderate severity requires either consultation by the primary care clinician with a mental health specialist or medication management, or both. At level 4, it is necessary to use specialized treatment programs or collaborative care, combining several modes of therapy. Level 5, the most severe and complex, requires a broad range of therapies and multiple disciplines coordinated by either the primary care clinician or the mental health specialist.

Patient preference also plays a role in treatment selection. Some patients respond best to a medical model approach that calls for directives from the physician as though managing a physical problem (Benjamin 1989). In a report from Germany on an inpatient approach to the treatment of chronic somatoform disorders in Turkish immigrants (Nickel et al. 2006), the authors recognize the importance of culture and language in guiding how specific groups of people conceptualize distress primarily through physical symptoms. Other patients respond better to a more psychotherapeutic approach that emphasizes the establishment of trust and formulation of the psychological aspects of the condition. A third approach, the reattribution approach, aims to help the patient reframe his or her physical distress by linking physical symptoms to physiological mechanisms and psychosocial stressors (Goldberg et al. 1989). Gradual thinning of the boundaries between physical and mental distress eventually contributes to a unified narrative for the various aspects of the disorder, leading to a reformulation of the case by the patient and clinician.

Providing Collaborative Care With Regular Appointments

The best framework for treating most somatic symptom disorders of moderate to severe complexity is a combination of primary care and mental health specialist appointments at regular intervals, with the two clinicians collaborating on a common treatment plan in the same clinical setting. This approach maximizes the opportunities for efficiently attending to the patient's somatic concerns while broadening the field of inquiry to psychosocial aspects of the illness. For

patients with high utilization rates, providing a schedule of regular appointments with each clinician (the frequency will vary with each patient and clinician) for the coming 3–6 months provides a framework for containing and managing distress, and this approach usually ends up reducing total utilization by minimizing urgent care behaviors (Hiller et al. 2003; Smith et al. 1986). As the stepped care model implies, the relative proportions of responsibility for care shared by the primary care clinician and the mental health specialists shift toward the specialist as the severity and complexity of the somatic disorder increase.

Affirming Explanations

The reattribution process begins with affirming the kernels of truth in the patient's somatic focus. By the time they reach the psychiatrist, most patients with chronic somatic symptom disorders have developed an acute sensitivity to being dismissed or disrespected. Until they feel they have earned the respect of the clinician, the alliance remains vulnerable. Therefore, it helps for the clinician to explicitly and repeatedly affirm the physical distress, the established physical disorders, and the alarming thoughts that are often triggered by somatic symptom patterns. Acknowledging the severity of the condition sets the stage for negotiating modest, achievable goals and lays the groundwork for systematic inquiry through symptom monitoring. As the therapy proceeds, the shared formulation can include a more sophisticated understanding of mechanisms of symptom formation, amplification, and denial or avoidance. At this level of behavioral specificity, it becomes possible to tailor specific treatments to specific behaviors (Looper and Kirmayer 2002).

Attending to the Doctor-Patient Relationship

Most patients with somatic symptom disorders who find their way to psychiatrists have experienced either dysfunctional or strained relationships with their primary care or specialty medical doctors. Early attention to the patterns of these relationships, with a focus on what derailed the relationships and what made them work well, is time well invested. Open discussion of these dynamics early on in the treatment benefits the task of developing a more resilient therapeutic alliance.

Monitoring Symptoms

Somatic symptom disorders share a useful feature: they are disorders of appraisal of somatic symptoms (Barsky and Ahern 2004). The distress is often rooted in misinterpretation of the meaning or severity of the physical signal. This cognitive distortion is not usually clear to the patient, and the patterns of dysfunctional appraisal that are at work in the patient's illness are not clear to the clinician in the beginning of treatment. A nonjudgmental approach to this feature of the condition involves engaging the patient in careful inquiry through daily monitoring of a few target symptoms to identify the patterns of key symptoms and responses to these patterns. The rationale for this approach rests on the observation that the cause and mechanisms for the patient's specific set of symptoms have not been established well enough to guide effective treatment. One test of the effectiveness of a treatment is whether it can reduce a specific symptom substantially and for an extended period of time, which relies on monitoring. This exercise also trains the patient to develop a consistent way of quantifying a symptom and its at-

tendant distress, arming both the patient and the clinician against the distortions of memory and illness beliefs.

Treating Comorbid Disorders

Before the clinician consolidates a treatment plan for a somatic symptom disorder, it is helpful to assess how much of the current somatic symptom pattern is the product of comorbid depression, anxiety, or insomnia. A careful history may suggest a sequence of events that helps in identifying which disorder came first or how much the somatic symptoms have been exacerbated by episodes of another disorder. Also, careful monitoring during effective treatment of an episode of depression or panic disorder, for example, often clarifies whether the patient suffers from one condition or two.

Medication Pruning

Once the therapeutic alliance has been established, it may be revealing to review the patient's medication list for redundancies or unnecessary side effects. Patients who have frustrated clinicians often end up with extra medications or excessive doses that cloud the picture or add to the somatic symptom profile. Reducing polypharmacy may clarify the nature of the somatic symptom disorder, but it often requires careful negotiation with patients about the meaning of the taper trial and the pace of the taper.

Modifying Social and Environmental Factors

When social and environmental factors contribute to the frequency or severity of the patient's symptoms, therapy can make quantum leaps forward by facilitating changes in such things as where the patient sleeps, whom the patient has to negotiate with daily, what toxins the patient is exposed to, and how much noise, heat, or violence the person has to tolerate.

Providing Patient Education

For any persistent or chronic condition that requires care rather than cure as the goal, a well-informed patient improves the chances for good and lasting outcomes. Key educational concepts include the basic connections between mind and body, the essentials of pain and pain management, and the role of stress in symptom amplification.

Outpatient Treatment Approaches

Combination Treatments

Under the umbrella of psychosomatic medicine, the group of disorders known in Europe as "functional somatic syndromes" (FSS) has been the subject of several reviews. In a narrative review, Henningsen et al. (2007) summarize the reviews and meta-analyses since 2001 that examined the range of management approaches to broadly defined FSS, which includes somatization disorder, hypochondriasis, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and multiple chemical sensitivities, among other subtypes. Across this range of syndromes, the researchers found a range of approaches effective, and they recommend a stepped care approach that differentiates between uncomplicated and complicated FSS. They conclude that nonpharmacological approaches "involving active participation of patients, such as exercise and psychotherapy, seem to be more effective than those that involve passive physical measures,

including injections and operations" (p. 953). Pharmacological agents with central nervous system effects are more effective than agents that target the peripheral physiological dysfunction. The authors recommend a balance of somatic and psychological interventions, including doctor-centered interventions to improve early recognition, communication, and avoidance of "harmful" tests and regimens.

In a similar effort with a narrower population focus, Häuser et al. (2009) reported on a meta-analysis of nine RCTs of 1,119 subjects with fibromyalgia who underwent "multicomponent therapy." In contrast to individual treatments, such as amitriptyline, duloxetine, CBT, and aerobic exercise, this multicomponent therapy had to include at least two nonpharmacological therapies (education, psychotherapy, exercise). The review reports strong evidence that multicomponent therapy reduces pain, fatigue, depressive symptoms, and limitations to health-related quality of life, and that it improves self-efficacy pain and physical fitness in the short term.

These reviews suggest that intensive treatments that combine multiple therapies should play a central role in the treatment of moderate to severe cases across the range of somatic symptom disorders.

Psychotherapy

Within the types of therapy for somatic symptom disorders, there is evidence for the efficacy of individual CBT and interpersonal therapy as well as group therapy and guided self-help.

Cognitive-Behavioral Therapy

A substantial number of high-quality studies have examined the role of CBT, whereas the number of reports on other types of therapy is small. Kroenke (2007) found that 11 of 13 studies of CBT in somatoform disorders reported significant improvements in at least one outcome for the CBT group compared to the control group. However, the number of studies of CBT in any one disorder ranged from one to five, so it is hard to draw conclusions about CBT applied to a specific somatoform disorder.

Barsky and Ahern (2004) assigned 187 patients and community volunteers with hypochondriasis to receive either usual medical care or experimental treatment (six 90-minute weekly CBT sessions plus a consultation letter to the primary care physician). Statistically significant improvements in the CBT group persisted at 6 and 12 months after the treatment, including lower levels of hypochondriacal symptoms, beliefs, attitudes, and health-related anxiety.

The cognitive therapy approach to somatic disorders begins with identifying the common dysfunctional automatic thoughts related to somatic symptom triggers. Common cognitive distortions include magnification, catastrophic thinking, and jumping to conclusions based on skimpy evidence. Therapeutic techniques include correcting faulty symptom attributions, restructuring beliefs and expectations about health and disease, modifying selected illness behaviors, and thought stopping or distractions from compulsive attention to benign symptoms.

Although much progress can be made in a few sessions, the course of CBT may extend for many months in more complex cases. Comprehensive CBT for somatic disorders relies also on psychoeducation, stress management, relaxation techniques, family and social network restructuring, modifying help-seeking behaviors, and supporting effective medication regimens.

Although often delivered in concert with antidepressant medications, CBT is a viable alternative for patients who choose to avoid medications. In one comparative study (Greeven et al. 2007), CBT outperformed paroxetine (45% vs. 30% response rate) in a sample of psychiatric outpatients with hypochondriasis.

Interpersonal Therapy

Interpersonal therapy (IPT) for somatic disorders has received relatively less scientific attention than CBT, but a recent report (Sattel et al. 2012) presents promising findings in a group of 211 patients with multisomatoform disorder recruited from outpatient medical clinics at six sites in Germany. These patients, who had no known medical or mental disorder, had a minimum of three current somatoform symptoms—pain, dizziness, bowel dysfunction, fatigue, and so on—that were functionally disabling for at least half the days over the previous 2 years and led to seeking medical help. In a 12-week parallel-group RCT of psychodynamic IPT versus enhanced medical care, the IPT group reported significantly better physical quality of life at 9-month follow-up. This protocol delivered therapy in three phases: 1) establishment of a trusting alliance, 2) linking of emotions and physical symptoms in the context of key relationships, and 3) termination. This study raises interesting possibilities for broadening the approach to somatic symptoms and for studying the cost effectiveness of a range of therapies.

Group Therapy

Schröder et al. (2012) recently reported on an RCT of group CBT versus enhanced medical care in 111 patients, ages 20–45, referred with functional somatic syndromes in Western Denmark. These patients had had at least 2 years of functional somatic symptoms ("bodily distress syndrome") from at least three of four bodily systems and moderate to severe impairment in daily living. Patients with other severe psychiatric or medical disorders were excluded. The group CBT was delivered by two psychiatrists in nine sessions over 12 weeks, each lasting 3.5 hours and having a relevant theme. Significant improvements were noted at 4 and 10 months after baseline. At 16-month follow-up, compared with the enhanced medical care group, the CBT intervention group had significantly greater improvement in the physical functioning, bodily pain, and vitality scales of the Short-Form 36-Item Health Survey (SF-36). This study represents the moderately intensive band of the specialty intervention spectrum, although less intense perhaps than some inpatient treatment programs. This study is the first to show a robust impact of an intensive group CBT intervention on a heterogeneous group of somatic symptom disorders. Further studies are needed to confirm this finding and examine the cost-effectiveness of intensive group interventions.

Guided Self-Help

When access to psychotherapy is limited, it is still possible to achieve symptom improvement through low self-management regimens prescribed by the primary care or specialist clinician. Sharpe et al. (2011) conducted an RCT of CBT-based guided self-help, compared to usual care, in a sample of neurology patients with "functional" neurological disorders. The intervention consisted of a self-help manual and four half-hour guidance sessions. At 3-month follow-up, compared to the usual care group, the guided self-help group reported significantly improved health on the Clinical Global Impression Scale. Symptoms and physical functioning remained im-

proved at the 6-month follow-up. This promising report requires confirmation, but it suggests that low-cost self-management regimens may serve the patient with functional neurological symptoms well when access to therapy is limited.

Somatic Therapies

The psychiatrist considering comprehensive treatment planning for patients with complex somatic symptom disorders should consider—in addition to psychotherapy and pharmacotherapy—graded exercise, physical therapy, and acupuncture. Early in the course of treatment, somatic therapies may prove more acceptable than psychosocial interventions to the patient who focuses predominantly on the physical aspects of distress.

Initially developed as an intervention for patients with chronic fatigue syndrome (Fulcher and White 1997), graded exercise regimens may be helpful for a range of somatic symptom disorders. Graded exercise begins at a low level of exercise, with scheduled rests between exercises. Through daily monitoring, the pacing of exercise and the rate of advancing is guided by fatigue levels, with the patient controlling the rate of advancing the regimen under the guidance of the therapist.

Physical therapy focused on reducing specific musculoskeletal symptoms may enhance a person's ability to engage in exercise and may help challenge dysfunctional assumptions about limitations on physical functioning.

Acupuncture may offer a useful adjunct to the management of somatic symptom disorders. In an RCT of acupuncture in "frequent attenders" at four general practices in London, England, Paterson et al. (2011) examined the effectiveness of adding individualized five-element acupuncture (at least 12 sessions) to usual care for 80 adults with medically unexplained symptoms who attended the office eight or more times per year. The acupuncture group reported improved health status compared to the usual care group at 26- and 52-week follow-ups. Although promising, these findings point to the need for more research to develop specific recommendations for types and durations of adjunctive acupuncture in patients with somatic symptom disorders.

Doctor-Centered Interventions

The troubled doctor-patient relationship, a common complication of the chronic course of somatic symptom disorders, has been the focus of several intervention studies. These studies, discussed in Chapter 33, underscore the value of the psychiatric consultant who attends to the primary care clinician's approach to the outpatient.

In inpatient settings, the priorities for the consulting psychiatrist include facilitating early recognition and diagnosis of somatic symptom disorders, education of nonpsychiatric clinicians about the principles of management, and providing guidance about avoiding harm through excessive investigations or counterproductive treatment efforts (Henningsen et al. 2007).

Inpatient Programs

Somatic symptom disorders are not a common primary diagnosis among psychiatric inpatients in the United States. Consequently, there are no model inpatient programs for the treatment of somatic symptom disorders in this country. However, in Germany and Japan, where psychosomatic medicine encompasses a broader range of psychiatric practice, so-

matic symptom disorders represent a substantial proportion of admissions to some general psychiatry units. One report on the history of psychosomatic medicine in Germany identified two general psychiatry units in which "somatoform disorders" constituted about one-fifth of all admissions (Diefenbacher 2005).

In a report from Bavaria, Germany, Nickel et al. (2006) described an inpatient program that specializes in psychosomatic disorders and provides a combination of psychopharmacology, individual therapy, and group therapy delivered during a 6-week period. The patients, 128 Turkish immigrants, participated in either "bioenergetic exercises" or light gymnastic exercises during the course of the RCT, which was designed to examine whether bioenergetics exercise significantly influenced the treatment results. For this group of patients, "somatization not only occurs as an alternative to expressions of psychological distress but also an accompaniment" (p. 508). The bioenergetics exercises focused on "vocal exercises, respiratory and bodily movement exercises, internal and external perception, expression of aggression, and grounding" (p. 509). The bioenergetics exercise group, compared to the light gymnastics group, reported significantly better results on psychological symptom checklists and self-report anxiety ratings at the end of the 6-week trial.

Conclusion

The approach to patients with chronic somatic symptoms begins with a plan for care, rather than cure. This care plan usually requires regular visits and multiple modes of treatment. A stepped care approach that accommodates the patient's preferences works best. Collaborative care with the primary care clinician reduces counterproductive evaluations or excessive treatments.

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PART VII

Sleep-Wake Disorders

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CHAPTER 36

Sleep-Wake Disorders

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This chapter includes treatments, for children and adults, of disorders subsumed under the category of sleep-wake disorders in DSM-5 (American Psychiatric Association 2013). The entire spectrum of treatment modalities for sleep disorders is too diverse for inclusion in such a brief chapter; we have, therefore, selected those that have a high level of empirical support and consensus among experts in the field and those that are most relevant in clinical practice.

Insomnia Disorder in Adults

DSM-5 diagnostic criteria for insomnia disorder appear in Box 36–1.

Box 36–1. DSM-5 Diagnostic Criteria for Insomnia Disorder

307.42 (F51.01)

A. A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:
   1. Difficulty initiating sleep. (In children, this may manifest as difficulty initiating sleep without caregiver intervention.)
   2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children, this may manifest as difficulty returning to sleep without caregiver intervention.)
   3. Early-morning awakening with inability to return to sleep.

B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.

C. The sleep difficulty occurs at least 3 nights per week.

D. The sleep difficulty is present for at least 3 months.

E. The sleep difficulty occurs despite adequate opportunity for sleep.
F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).
G. The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).
H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

Specify if:

With non–sleep disorder mental comorbidity, including substance use disorders
With other medical comorbidity
With other sleep disorder

Coding note: The code 780.52 (G47.00) applies to all three specifiers. Code also the relevant associated mental disorder, medical condition, or other sleep disorder immediately after the code for insomnia disorder in order to indicate the association.

Specify if:

Episodic: Symptoms last at least 1 month but less than 3 months.
Persistent: Symptoms last 3 months or longer.
Recurrent: Two (or more) episodes within the space of 1 year.

Note: Acute and short-term insomnia (i.e., symptoms lasting less than 3 months but otherwise meeting all criteria with regard to frequency, intensity, distress, and/or impairment) should be coded as an other specified insomnia disorder.

Nonpharmacological Interventions

Psychological and behavioral therapies for insomnia are listed in Table 36–1 (Morgenthaler et al. 2006). When compared with pharmacological methods, they have the advantage of longer duration of benefit (Morin et al. 2006).

Sleep hygiene education (Table 36–2) strives to correct behaviors that are harmful to sleep. Sleep hygiene education is unlikely to resolve insomnia when used alone, yet it is considered to be a necessary component of any nonpharmacological strategy because poor sleep hygiene habits may impair the effectiveness of other therapeutic techniques (Hauri 2012).

Guidelines for stimulus control therapy and sleep restriction therapy are outlined in Tables 36–3 and 36–4, respectively (Yang et al. 2006).

Sleep-focused cognitive-behavioral therapy (SCBT) combines various elements of these nonpharmacological strategies, as noted earlier in Table 36–1. Unlike many forms of therapy, SCBT for insomnia is structured, time-limited, and focused on insomnia and other sleep-related issues. Optimally, the various combinations of therapies should be tailored to the patient's specific symptoms and other clinical characteristics; however, because such guidelines are lacking, SCBT combines multiple dimensions to enhance effectiveness. Sessions are typically conducted once per week over the course of 6–8 weeks, although frequency and length of treatment may need to be augmented if the clinical picture is complicated by the presence of comorbid conditions, the combined use of hypnotics, low patient motivation, and high levels of distress. The usefulness of SCBT has also been demonstrated in the context of comorbidities such as alcoholism, fibromyalgia, Alzheimer's disease, osteoarthritis, and chronic obstructive pulmonary disease (COPD) (Stepanski and Rybarczyk 2006).

TABLE 36–1. Psychological and behavioral therapies for insomnia

Intervention	Goal	Method
Sleep hygiene education	Promote habits that help sleep; eliminate habits that interfere with sleep	Promote habits that help sleep; eliminate habits that interfere with sleep
Stimulus control therapy[a]	Strengthen bed and bedroom as sleep stimuli	If unable to fall asleep within 20 minutes, get out of bed and repeat as necessary
Restriction of time in bed (sleep restriction)	Improve sleep continuity by limiting time spent in bed	Decrease time in bed to equal time actually asleep and increase as sleep efficiency improves
Cognitive therapy	Dispel faulty and maladaptive beliefs that may perpetuate insomnia	Use talk therapy to dispel unrealistic and exaggerated notions about sleep
Relaxation therapies[a]	Reduce arousal and decrease anxiety	Use biofeedback, progressive muscle relaxation
Paradoxical intention	Relieve performance anxiety	Instruct patient to try to stay awake
Sleep-focused cognitive-behavioral therapy[a]	Address multiple dimensions of insomnia to enhance effectiveness	Combine sleep restriction, stimulus control, and sleep hygiene education with cognitive therapy

[a]Standard therapy (high clinical certainty).

SCBT has been shown to have durability of benefit for up to 6 months following the termination of treatment (Morin et al. 2006), which clearly distinguishes it from pharmacotherapy, for which evidence of lasting benefit is lacking. The major drawbacks of SCBT, relative to pharmacotherapy, lie in its greater reliance on patient initiative, motivation, and active participation in the treatment process; patients' ability to accept the notion of delayed gratification; greater time commitment; and limited availability of practitioners. Future trends in treatment that are beginning to address some of these drawbacks include the development of group SCBT, providing SCBT training for primary care nurse practitioners and nurses in primary care settings, and providing treatment through telemedicine (Ritterband et al. 2009).

Pharmacological Agents

FDA-Approved Hypnotic Agents

Hypnotic agents approved by the U.S. Food and Drug Administration (FDA) are summarized in Table 36–5 (Markov and Doghramji 2010; Neubauer 2012; Transcept Pharmaceuticals 2012). Some of these agents are effective for sleep initiation, some for sleep maintenance, and some for both. All should be administered at bedtime, except zolpidem sublingual 3.5 or 1.75 mg can also be administered

TABLE 36–2. Elements of sleep hygiene education

Do the following:
Awaken at the same time every morning
Increase exposure to bright light during the day
Establish a daily activity routine
Exercise regularly in the morning and/or afternoon
Set aside a worry time
Establish a comfortable sleep environment
Do something relaxing prior to bedtime
Try a warm bath
Avoid the following:
Napping, unless a shift worker
Alcohol
Caffeine, nicotine, and other stimulants
Exposure to bright light during the night
Exercise within 3 hours of bedtime
Heavy meals or drinking within 3 hours of bedtime
Noise
Excessive heat or cold in room
Using bed for things other than sleep (or sex)
Watching the clock
Trying to sleep

TABLE 36–3. Guidelines for stimulus control therapy

Go to bed only when sleepy.
Use bed for sleep and sex only; avoid watching television, reading, or eating in bed.
If unable to fall asleep in 15 minutes, then as soon as anxiety or irritability begins, leave the bedroom and go to another room. Do not watch the clock.
Return to bed only when sleepy.
Repeat above tactic as often as needed.
Regardless of total sleep time, always wake up at the same time.
Avoid daytime naps.

following middle-of-the-night awakenings only if patients have the opportunity to be in bed for at least 4 hours after administration.

Adverse effects of the benzodiazepine receptor agonists include daytime sedation and psychomotor and cognitive impairment. Hypnotics should be used with caution in individuals with respiratory depression (e.g., COPD and obstructive sleep apnea hypopnea [OSAH]), hepatic disease, or multiple medical conditions; in elderly patients; and in those who are taking other medications that have central nervous system–depressant properties. Individuals who must awaken during the

TABLE 36–4. Guidelines for sleep restriction therapy

Determine average time spent asleep by keeping a 1- to 2-week sleep diary.
Set time in bed to equal time spent asleep, never less than 5 hours.
Determine mean sleep efficiency (time spent asleep ÷ [time in bed] × 100 = %) over 5-day period.
If efficiency is ≥90%, increase time in bed by 15–20 minutes.
If efficiency is <85%, decrease time in bed by 15–20 minutes.
Maintain regular wake time.
Take no naps.

course of the drug's active period should not take these medications (Doghramji and Doghramji 2006; Neubauer 2012).

Adverse effects of ramelteon include somnolence, fatigue, and dizziness. It should not be administered with fluvoxamine because of a cytochrome P450 (CYP) 1A2 interaction. A mild elevation in prolactin levels has been noted in a small number of females, and a mild decrease in testosterone values has been noted in elderly males; however, the clinical relevance of these changes remains unclear. Ramelteon does not demonstrate respiratory depression in mild to moderate OSAH or in mild to moderate COPD (Zammit et al. 2007).

The most common adverse effects associated with low-dose doxepin are somnolence/sedation, nausea, and upper respiratory tract infection. At higher, antidepressant doses, doxepin is associated with anticholinergic side effects, including sedation, confusion, urinary retention, constipation, blurred vision, and dry mouth, and other effects such as hypotension and dose-dependent cardiotoxicity; nevertheless, these effects are not observed at hypnotic doses. Doxepin is contraindicated in patients with severe urinary retention or narrow-angle glaucoma and in those who have used monoamine oxidase inhibitors within the previous 2 weeks (Markov and Doghramji 2010).

The risk of rebound insomnia and withdrawal symptoms can be minimized by using the lowest effective dose and by gradually tapering the dose over the course of a few nights. These effects appear to be more pronounced following the administration of older benzodiazepine agents that have a short elimination half-life, such as triazolam, than the longer-elimination half-life benzodiazepines and some of the newer benzodiazepine receptor agonist nonbenzodiazepines (Soldatos et al. 1999). Eszopiclone (Krystal et al. 2003), extended-release zolpidem (Krystal et al. 2008), and ramelteon (Mayer et al. 2009) have been evaluated for up to 6 months in controlled studies and have demonstrated a low proclivity for the production of these effects. Nevertheless, clinical wisdom suggests that all hypnotics should be used for short periods of time as much as possible.

Hypnotics carry the potential for severe allergic reactions and complex sleep-related behaviors, which include sleep driving. The latter may be associated with concomitant ingestion of alcohol and other sedating substances (Southworth et al. 2008).

Hypnotics should be used at reduced dosages in elderly patients, and whenever possible those with the shortest half-lives should be considered. The BzRAs should not be offered to patients with a history of drug and alcohol dependence

TABLE 36–5. Hypnotic agents approved by the U.S. Food and Drug Administration

Class	Hypnotic	Dose (mg)	Elimination half-life (hours)	Indications	DEA schedule
Benzodiazepine receptor agonist benzodiazepines	Flurazepam	15, 30	48–120	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakening.	IV
	Temazepam	7.5, 15, 22.5, 30	8–20	Short-term treatment of insomnia.	IV
	Triazolam	0.125, 0.25	2–4	Short-term treatment of insomnia.	IV
	Quazepam	7.5, 15	48–120	Treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.	IV
	Estazolam	1, 2	8–24	Short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings…administered at bedtime improved sleep induction and sleep maintenance.	IV

TABLE 36–5. Hypnotic agents approved by the U.S. Food and Drug Administration *(continued)*

Class	Hypnotic	Dose (mg)	Elimination half-life (hours)	Indications	DEA schedule
Benzodiazepine receptor agonist nonbenzodiazepines	Zolpidem	5, 10	1.5–2.4	Short-term treatment of insomnia characterized by difficulties with sleep initiation.	IV
	Zaleplon	5, 10	1	Short-term treatment of insomnia…shown to decrease the time to sleep onset.	IV
	Eszopiclone	1, 2, 3	5–7	Treatment of insomnia…administered at bedtime decreased sleep latency and improved sleep maintenance.	IV
	Zolpidem ER	6.25, 12.5	2.8–2.9	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset).	IV
	Zolpidem oral spray	5, 10	2.7	Short-term treatment of insomnia characterized by difficulties with sleep initiation.	IV
	Zolpidem sublingual	5, 10	2.9	Short-term treatment of insomnia characterized by difficulties with sleep initiation.	IV
	Zolpidem sublingual	Men: 3.5 Women: 1.75	2.5	Use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep. Limitation of use: not indicated for the treatment of middle-of-the-night awakening when the patient has fewer than 4 hours of bedtime remaining before the planned time of waking.	IV
Melatonin receptor					None

without close monitoring. The addition of alcohol and other sedating agents may lead to potentiation of sedative effects and a decreased margin of safety. Recently, the U.S. Food and Drug Administration (2013) recommended that the doses of zolpidem preparations that are approved for bedtime use be lowered because new data indicate that blood levels in some patients, particularly women, may be high enough the morning after use to impair activities that require alertness, including driving. For women, the FDA recommended 5 mg for immediate-release products (zolpidem, zolpidem oral spray, and zolpidem sublingual) and 6.25 mg for zolpidem extended-release (ER). The recommended doses of low-dose zolpidem sublingual, utilized for middle-of-the-night awakenings, remain unchanged at 3.5 mg for men and 1.75 mg for women.

Non-FDA-Approved Medications

The evidence supporting the use in patients with insomnia of sedating antidepressants, such as trazodone and mirtazapine, or of antipsychotic agents, typically at low doses that are subtherapeutic from the standpoint of their intended applications, is scant (James and Mendelson 2004; National Institutes of Health 2005); therefore, the FDA has not approved these drugs for insomnia. Although trazodone does increase total sleep time in patients with major depressive disorder, there are virtually no dose-response data for trazodone in regard to sleep and, similarly, no available data on tolerance to its possible hypnotic effects. Concerns have been raised regarding daytime somnolence, the significant dropout rates in clinical studies, and the induction of cardiac arrhythmias, primarily in patients with histories of cardiac disease, as well as the development of priapism. Sedating antipsychotic agents have also received little scientific attention for the management of insomnia, and their spectrum of potential side effects includes sedation and metabolic disturbances; their use in primary insomnia cannot, therefore, be wholeheartedly supported.

Over-the-Counter Agents

Over-the-counter agents marketed for insomnia contain the antihistamines diphenhydramine or doxylamine. Although the evidence supporting their efficacy in insomnia is scant, antihistamines may produce mild to moderate sedation and may improve sleep latency and continuity for some individuals. However, tolerance to their sedating effects can develop rapidly (Richardson et al. 2002). Diphenhydramine is also associated with morning grogginess, daytime sleepiness possibly leading to impairment of driving ability, delirium, urinary retention, constipation, dry mouth, blurry vision, and psychomotor impairment (Basu et al. 2003).

Although their use is not regulated by the FDA, dietary supplements and herbal remedies also enjoy extensive usage, owing to a variety of factors, including their widespread availability, lack of prescription requirements, relatively low cost, and the widespread belief that they are safe and have a relatively low abuse risk. These include, among others, valerian, kava-kava (*Piper methysticum*), melatonin, chamomilla, passiflora, *Avena sativa,* and *Humulus lupulus.* Most of these have not been well studied for safety and efficacy; melatonin, which has received the widest evaluations, may be effective in the treatment of delayed sleep phase disorder and shift work disorder but does not appear to be consistently effective in treating most primary or comorbid sleep disorders with short-term use (Buscemi et al. 2004; National Institutes of Health 2005).

Not all adverse effects of all hypnotic agents have been thoroughly reviewed here. Readers are referred to the end-of-chapter references for further information.

Selection of Treatment Modality

Hypnotic agents and SCBT are generally equally effective in addressing insomnia, but SCBT may be more effective in reducing latency to sleep onset (Smith et al. 2002). The improvement sustained by medication tends to be rapid, yet this improvement is lost rapidly after drug discontinuation. On the other hand, benefit derived from SCBT is slower yet well sustained long after the discontinuation of treatment (Morin et al. 1999, 2009; Sivertsen et al. 2006).

Although there are no guidelines as to which therapeutic modality—hypnotics or SCBT—is more appropriate for a given clinical situation, the identification of psychological factors (e.g., increase in tension and anxiety with the approach of bedtime), cognitive factors (e.g., focus on the catastrophic consequences of poor sleep), and behavioral factors (e.g., excessive caffeine consumption and irregular bedtimes) in insomnia may favor the initiation of treatment with SCBT. As noted, SCBT requires considerable patient participation in the treatment process and an ability to delay gratification, and the lack of these two essential ingredients favors the use of pharmacotherapy. On the other hand, the need for rapid symptomatic improvement favors pharmacotherapy as the initial option. The two treatment modalities can be combined to maximize response, although studies in this area are preliminary in nature. SCBT can also be of assistance in tapering and discontinuing hypnotic medications in long-term users of hypnotics (Zavesicka et al. 2008), and combination therapies may be useful in enhancing compliance to either treatment alone.

Insomnia Disorder in Children and Adolescents

Nonpharmacological Interventions

Childhood insomnias typically present with behavioral disturbances such as bedtime resistance and refusal and conflicts between parents and children over bedtime. For this and other reasons, nonpharmacological interventions should almost always be considered first in the treatment of insomnia disorder in pediatric patients (Kuhn and Elliott 2003; Meltzer and Mindell 2004; Mindell et al. 2006). Prior to the initiation of interventions, parents and children should be educated regarding normal sleep requirements, and realistic parent and child treatment goals should be established. School schedules and extracurricular activities should be taken into consideration when establishing treatment protocols. It is very important to set, and consistently reinforce, age-appropriate and consistent bedtimes and rise times and to use bedtime routines to provide behavioral cues for transition to sleep. Morning rise time is especially important as a powerful environmental cue for entrainment of the sleep-wake cycle. Nonpharmacological interventions are summarized in Table 36–6 (Bootzin and Stevens 2005).

Pharmacological Agents

Although no pharmacological agents have received FDA approval for pediatric insomnia, physicians have been using such agents on an off-label basis at in-

TABLE 36–6. Nonpharmacological interventions for pediatric insomnia

Intervention	Method
Sleep education	Provide information on purpose of sleep, organization of sleep states, and sleep norms for different age groups.
Positive bedtime routine	Establish relaxing, low-stress, low-conflict interactions between parent and child starting 30 minutes before lights out. Introduce a transitional object (a toy, a blanket) that can take place of parent or other maladaptive sleep-onset associations.
Sleep hygiene	Educate child and parent to engage in sleep-conducive behaviors prior to bedtime and to ensure that bedroom environment favors sleep. Electronic media (television, video games, cell phones) and pets should be eliminated from the bedroom prior to bedtime. Lights and noise should be attenuated.
Appropriate sleep scheduling	Modify sleep schedule if child's bedtime is exceedingly early or late or if nap times interfere with bedtime. Select age-appropriate sleep schedule for child and teach parents how to implement it. Bedtimes and rise times should be kept constant.
Unmodified extinction	Instruct parents to immediately mitigate reinforcing factors, such as temper tantrums at bedtime, by consistently ignoring child's disruptive behavior at bedtime.
Graduated extinction	Instruct parents to gradually reduce their presence in the bedroom or their attention to inappropriate bedtime behaviors. Typically, extinction is combined with periodic "check-ins."
Extinction with parental presence	Recommend that parent remain in child's bedroom while ignoring disruptive behavior at bedtime. Parent may leave room after child falls asleep. Child's awareness of parent's presence in bedroom reduces separation anxiety, making this approach less difficult to implement than prior two approaches.
Scheduled awakenings	Address frequent nocturnal awakenings by establishing pretreatment pattern of nocturnal awakenings, then instructing parents to awaken child 15–30 minutes prior to anticipated spontaneous awakenings. Scheduled awakenings are then gradually delayed until child sleeps through night.
Relaxation training	Teach children and adolescents to identify symptoms associated with increased somatic and cognitive tension that can delay sleep onset. Progressive muscle relaxation and diaphragmatic breathing can help to reduce somatic tension and to facilitate sleep onset.

creasing rates (Owens et al. 2003, 2010), highlighting the clinical need for such agents. The extent of use of such agents, and concerns regarding the lack of FDA guidelines, prompted the formation of an American Academy of Sleep Medicine task force to formulate clinical guidelines for the use of sedative-hypnotics in children. Some of these guidelines are listed in Table 36–7.

TABLE 36–7. Selected guidelines for use of pharmacological agents for treatment of pediatric insomnia

Establish the best possible match between the clinical condition and the individual properties of currently available medications.
Screen patients for concurrent use of nonprescription sleep aids, alcohol, and illicit drugs.
Conduct a thorough risk-benefit analysis in the context of the clinical situation.
Avoid use of medications with central nervous system–depressant properties in the presence of untreated conditions that may be aggravated by them, such as sleep apnea syndrome.
Always use medication in combination with behavioral interventions.
Establish realistic yet well-defined treatment goals that are agreed on by family members prior to initiation of treatment.
Use medications for short periods of time as much as possible and conduct regular follow-up evaluations.

Pharmacological agents and selected clinical properties are listed in Table 36–8. At a dose of 0.25 mg/kg (max 10 mg), zolpidem failed to reduce latency to persistent sleep in children and adolescents with insomnia associated with ADHD (Blumer et al. 2009). At doses up to 3 mg, eszopiclone was generally well tolerated by pediatric patients but failed to reduce latency to persistent sleep in children ages 6–17 years with ADHD-associated insomnia (Zammit et al. 2012).

Hypersomnolence Disorder

DSM-5 diagnostic criteria for hypersomnolence disorder appear in Box 36–2. Treatment principles for this disorder are similar to those for narcolepsy, which is discussed in the following section.

Box 36–2. DSM-5 Diagnostic Criteria for Hypersomnolence Disorder

307.44 (F51.11)

A. Self-reported excessive sleepiness (hypersomnolence) despite a main sleep period lasting at least 7 hours, with at least one of the following symptoms:
   1. Recurrent periods of sleep or lapses into sleep within the same day.
   2. A prolonged main sleep episode of more than 9 hours per day that is nonrestorative (i.e., unrefreshing).
   3. Difficulty being fully awake after abrupt awakening.

TABLE 36–8. Pharmacological agents for pediatric insomnia

Drug	Dose range[a]	Mechanism of action	Safety profile	Effects on sleep	Other uses in children[b]
Clonazepam	0.25–2 mg	GABA agonist	Strong abuse potential	Suppresses SWS; reduces frequency of arousals	Partial arousals (sleepwalking, night terrors, REM sleep behavior disorder)
Clonidine	0.025–0.3 mg; increase by 0.05-mg increments	α_2 Agonist	Narrow therapeutic index; dry mouth, bradycardia, hypotension; hypertension following abrupt discontinuation	Decreases SOL	Sleep onset and maintenance disturbances, ADHD
Guanfacine	0.5–2 mg	α_2 Agonist	Same as for clonidine but less sedating	Same as for clonidine	Same as for clonidine
Diphenhydramine	25–50 mg (do not exceed 300 mg/day)	Histamine H_1 agonist; crosses blood-brain barrier	In overdose may cause hallucinations, seizures, agitation	Reduces SOL; improves sleep continuity in children	Mild sedative effect; high level of parental acceptance
Trazodone	25–100 mg	Serotonin 5-HT agonist and reuptake inhibitor, blocks histamine receptors	Priapism, orthostatic hypotension, dizziness	Increases SWS; reduces SOL	Insomnia with comorbid depression and anxiety disorders
Mirtazapine	7.5–15 mg	Serotonin 5-HT_2, 5-HT_3 antagonist, muscarinic antagonist, histamine H_1 receptor antagonist	Increased appetite, weight gain, dry mouth	Reduces SOL, increases sleep duration	Insomnia with comorbid depression (at low doses)

TABLE 36–8. Pharmacological agents for pediatric insomnia *(continued)*

Drug	Dose range[a]	Mechanism of action	Safety profile	Effects on sleep	Other uses in children[b]
Melatonin	0.3–6 mg	Melatonin MT_1 and MT_2 agonist	Not well defined	Decreases SOL	Insomnia with comorbid autism spectrum disorder, developmental disabilities, ADHD, blindness, neurological impairments
Zolpidem	5–10 mg	BZRA	Sleep-related behaviors, retrograde amnesia, headaches, dizziness, residual sedation; has abuse potential	Decreases SOL; little to no effect on sleep architecture	Insomnia with comorbid ADHD
Eszopiclone	1–3 mg	BZRA	Same as for zolpidem	Decreases SOL and WASO; little to no effect on sleep architecture	Insomnia with comorbid ADHD

Note. ADHD=attention-deficit/hyperactivity disorder; BZRA=benzodiazepine receptor agonist; GABA=γ-aminobutyric acid; REM=rapid eye movement; SOL=sleep onset latency; SWS=slow wave sleep; WASO=wake after sleep onset.
[a]Doses of these drugs have not been evaluated in children for the indication of insomnia.
[b]Not approved for these uses by the U.S. Food and Drug Administration.

B. The hypersomnolence occurs at least three times per week, for at least 3 months.
C. The hypersomnolence is accompanied by significant distress or impairment in cognitive, social, occupational, or other important areas of functioning.
D. The hypersomnolence is not better explained by and does not occur exclusively during the course of another sleep disorder (e.g., narcolepsy, breathing-related sleep disorder, circadian rhythm sleep-wake disorder, or a parasomnia).
E. The hypersomnolence is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).
F. Coexisting mental and medical disorders do not adequately explain the predominant complaint of hypersomnolence.

Specify if:

With mental disorder, including substance use disorders
With medical condition
With another sleep disorder

Coding note: The code 780.54 (G47.10) applies to all three specifiers. Code also the relevant associated mental disorder, medical condition, or other sleep disorder immediately after the code for hypersomnolence disorder in order to indicate the association.

Specify if:

Acute: Duration of less than 1 month.
Subacute: Duration of 1–3 months.
Persistent: Duration of more than 3 months.

Specify current severity:

Specify severity based on degree of difficulty maintaining daytime alertness as manifested by the occurrence of multiple attacks of irresistible sleepiness within any given day occurring, for example, while sedentary, driving, visiting with friends, or working.

Mild: Difficulty maintaining daytime alertness 1–2 days/week.
Moderate: Difficulty maintaining daytime alertness 3–4 days/week.
Severe: Difficulty maintaining daytime alertness 5–7 days/week.

Narcolepsy

Narcolepsy, whose diagnostic criteria appear in Box 36–3, is an incurable neurological disorder that persists for life. Therefore, lifelong management is typically needed. Prior to treatment, a thorough diagnostic evaluation in a sleep disorders center is critical to ensure diagnostic accuracy and to avoid lifelong treatment with highly controlled medications. Behavioral measures should always be used because they can decrease the degree of reliance on medications and enhance medication effectiveness (Rogers et al. 2001). These include maintenance of good sleep hygiene habits (see Table 36–2), avoidance of sleep deprivation, taking daily scheduled naps, avoidance of alcohol and recreational substances, and avoidance of stimulant substances close to bedtime. Driving safety should be assessed and, if sleepiness is severe, patients should be advised to avoid driving and engaging in other potentially dangerous activities when sleepy. If sleepy while driving, patients can be advised to stop driving and take a nap. Physicians should be knowledgeable about state requirements for reporting patients who are assessed as posing a driving risk to the department of motor vehicles. In addition, career counseling for patients, as well as education for their employers, is often necessary.

Box 36–3. DSM-5 Diagnostic Criteria for Narcolepsy

A. Recurrent periods of an irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day. These must have been occurring at least three times per week over the past 3 months.

B. The presence of at least one of the following:

1. Episodes of cataplexy, defined as either (a) or (b), occurring at least a few times per month:
   a. In individuals with long-standing disease, brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking.
   b. In children or in individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers.
2. Hypocretin deficiency, as measured using cerebrospinal fluid (CSF) hypocretin-1 immunoreactivity values (less than or equal to one-third of values obtained in healthy subjects tested using the same assay, or less than or equal to 110 pg/mL). Low CSF levels of hypocretin-1 must not be observed in the context of acute brain injury, inflammation, or infection.
3. Nocturnal sleep polysomnography showing rapid eye movement (REM) sleep latency less than or equal to 15 minutes, or a multiple sleep latency test showing a mean sleep latency less than or equal to 8 minutes and two or more sleep-onset REM periods.

Specify whether:

347.00 (G47.419) Narcolepsy without cataplexy but with hypocretin deficiency: Criterion B requirements of low CSF hypocretin-1 levels and positive polysomnography/multiple sleep latency test are met, but no cataplexy is present (Criterion B1 not met).

347.01 (G47.411) Narcolepsy with cataplexy but without hypocretin deficiency: In this rare subtype (less than 5% of narcolepsy cases), Criterion B requirements of cataplexy and positive polysomnography/multiple sleep latency test are met, but CSF hypocretin-1 levels are normal (Criterion B2 not met).

347.00 (G47.419) Autosomal dominant cerebellar ataxia, deafness, and narcolepsy: This subtype is caused by exon 21 DNA (cytosine-5)-methyltransferase-1 mutations and is characterized by late-onset (age 30–40 years) narcolepsy (with low or intermediate CSF hypocretin-1 levels), deafness, cerebellar ataxia, and eventually dementia.

347.00 (G47.419) Autosomal dominant narcolepsy, obesity, and type 2 diabetes: Narcolepsy, obesity, and type 2 diabetes and low CSF hypocretin-1 levels have been described in rare cases and are associated with a mutation in the myelin oligodendrocyte glycoprotein gene.

347.10 (G47.429) Narcolepsy secondary to another medical condition: This subtype is for narcolepsy that develops secondary to medical conditions that cause infectious (e.g., Whipple's disease, sarcoidosis), traumatic, or tumoral destruction of hypocretin neurons.

Coding note (for ICD-9-CM code 347.10 only): Code first the underlying medical condition (e.g., 040.2 Whipple's disease; 347.10 narcolepsy secondary to Whipple's disease).

Specify current severity:

Mild: Infrequent cataplexy (less than once per week), need for naps only once or twice per day, and less disturbed nocturnal sleep.

Moderate: Cataplexy once daily or every few days, disturbed nocturnal sleep, and need for multiple naps daily.

Severe: Drug-resistant cataplexy with multiple attacks daily, nearly constant sleepiness, and disturbed nocturnal sleep (i.e., movements, insomnia, and vivid dreaming).

Behavioral treatments alone can suffice for some individuals with narcolepsy; however, chronic treatment with pharmacological agents is often necessary. A dual approach should be considered, with stimulants for excessive daytime sleepiness (EDS) and rapid eye movement (REM)–suppressing agents for auxiliary symptoms such as cataplexy, hypnagogic hallucinations, and sleep paralysis (Morgenthaler et al. 2007; Wise et al. 2007).

Pharmacological agents used in the treatment of narcolepsy are listed in Table 36–9 (Guilleminault and Cao 2011). The relative efficacy of these agents has not been adequately explored. Longer-acting stimulants (e.g., modafinil, armodafinil, sustained-release amphetamine) can provide all-day benefit following morning administration. However, stimulants with a short duration of action (e.g., methylphenidate) can be used in combination to achieve alertness quickly on an as-needed basis. Short-acting stimulants can also be administered later in the day with less concern regarding insomnia. Stimulants, with the exception of modafinil and armodafinil, can also provide mild anticataplectic effects. However, the addition of an REM suppressant is often necessary. γ-Hydroxybutyrate (GHB) has positive effects both for cataplexy and for EDS. Because it is a potent sedative, however, GHB should be administered at bedtime, after the patient is already in bed, to avoid mishaps due to motor impairment. A second dose is administered 2–3 hours later, again while the patient is in bed.

Side effects associated with the stimulants include irritability, talkativeness, sweating, headaches, nervousness, tremulousness, anorexia, insomnia, gastrointestinal complaints, dyskinesias, and palpitations. Psychotic symptoms such as hallucinations may be more common in individuals with a history of psychiatric disorders. Tolerance to stimulants, although possible, has not been well described in patients with narcolepsy. The most common side effects of modafinil and armodafinil are headache, nausea, and nervousness or anxiety. Serious rashes, including Stevens-Johnson syndrome, have been reported with the use of modafinil and armodafinil; duration of therapy cannot be relied on as a means to predict the potential risk of rash. Therefore, these agents should be discontinued at the first sign of rash. The effectiveness of steroidal contraceptives may be reduced with these agents, and alternative methods of contraception may be considered. GHB's most common side effects are disorientation and sedation if patients awaken during the course of the night. Also reported are enuresis, nausea, and somnambulism. Because GHB has potent sedative properties, it should not be used with alcohol or other central nervous system depressants or in patients with untreated obstructive sleep apnea syndrome. GHB has high sodium content and therefore should not be used by individuals with compromised renal function, uncontrolled hypertension, or unstable cardiac failure (Physician's Desk Reference 2013).

TABLE 36–9. Pharmacological agents for narcolepsy

	Medication	Total daily dose	DEA schedule
Excessive daytime sleepiness	Armodafinil	50–250 mg	IV
	Atomoxetine[a]	10–25 mg	None
	Dextroamphetamine	5–60 mg	II
	Methamphetamine[a]	20–25 mg	II
	Methylphenidate[a]	10–60 mg	II
	Modafinil	100–400 mg	IV
	Sodium oxybate (γ-hydroxybutyrate)	6–9 g[b]	III
Cataplexy	Clomipramine[a]	25–200 mg	None
	Desipramine[a]	25–200 mg	None
	Fluoxetine[a]	20–60 mg	None
	Imipramine[a]	25–200 mg	None
	Protriptyline[a]	2.5–20 mg	None
	Sodium oxybate (γ-hydroxybutyrate)	6–9 g[b]	III
	Venlafaxine[a]	75–300 mg	None
	Viloxazine[a]	50–200 mg	None

[a]Not approved for this use by the U.S. Food and Drug Administration.
[b]Administered at bedtime, divided into two doses.

Considerations in Children

Although many of the agents described in the previous paragraphs are utilized in children, their use in children and adolescents has not been established with double-blind, placebo-controlled studies. No medications have FDA approval for treatment of narcolepsy in children and adolescents. One uncontrolled study with a small sample of children suggested that modafinil may have a modest effect on EDS (Ivanenko et al. 2003). The suggested dose range for children is 50–200 mg/day in divided doses and 200–400 mg/day for adolescents. Because of reported skin reactions in children, including one case of possible erythema multiforme/Stevens-Johnson syndrome, modafinil should be used with caution in pediatric patients (Physician's Desk Reference 2013). Retrospective reviews also suggest that sodium oxybate can be useful for the management of excessive sleepiness and cataplexy (Aran et al. 2010) and that antidepressants can be useful for cataplexy. The latter include selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, serotonin-norepinephrine reuptake inhibitors such as venlafaxine, and noradrenergic reuptake inhibitors such as atomoxetine (Billiard 2008).

Breathing-Related Sleep Disorders

Obstructive Sleep Apnea Hypopnea

Diagnostic criteria for OSAH are listed in Box 36–4, and treatment modalities are listed in Table 36–10 (Kryger et al. 2011).

Behavioral measures should be considered for treatment of OSAH, although they are seldom used in isolation. Weight loss should be encouraged because population studies show a direct relationship between weight loss and lower illness severity (Peppard et al. 2000). The most widely used initial treatment approach is the application of nasal continuous positive airway pressure (CPAP) during sleep (Kushida et al. 2006). The pressure necessary to effectively manage breathing disturbances can be determined through a sleep laboratory study or through autotitration devices. CPAP treatment generally improves hallmark symptoms of the disorder, such as EDS, cognitive impairment, sleep discontinuity, snoring, and breathing pauses during sleep. It has also been shown to improve mood-related measures (Schwartz and Karatinos 2007), and long-term studies suggest that it decreases mortality associated with the condition (Campos-Rodriguez et al. 2005). The primary limitation of CPAP therapy is compliance; the device must be worn during the entire sleep period, including naps, to ensure maximal efficacy. CPAP machines that monitor and store information regarding daily usage time are desirable to provide an objective measure of compliance rates. These devices can also provide estimates of the frequency of breathing pauses during sleep, allowing clinicians to make adjustments to maximize effectiveness. The most common complaints leading to noncompliance relate to the mask interface (mask tightness, bridge-of-nose pain, facial indentations, air leakage, etc.). Other adverse experiences include nasal congestion, dryness, rhinorrhea, claustrophobic air swallowing, and chest discomfort.

Box 36–4. DSM-5 Diagnostic Criteria for Obstructive Sleep Apnea Hypopnea

327.23 (G47.33)

A. Either (1) or (2):

1. Evidence by polysomnography of at least five obstructive apneas or hypopneas per hour of sleep and either of the following sleep symptoms:
   a. Nocturnal breathing disturbances: snoring, snorting/gasping, or breathing pauses during sleep.
   b. Daytime sleepiness, fatigue, or unrefreshing sleep despite sufficient opportunities to sleep that is not better explained by another mental disorder (including a sleep disorder) and is not attributable to another medical condition.
2. Evidence by polysomnography of 15 or more obstructive apneas and/or hypopneas per hour of sleep regardless of accompanying symptoms.

Specify current severity:

Mild: Apnea hypopnea index is less than 15.
Moderate: Apnea hypopnea index is 15–30.
Severe: Apnea hypopnea index is greater than 30.

TABLE 36–10. Therapies for obstructive sleep apnea hypopnea

Behavioral measures	Avoidance of central nervous system depressants
	Reducing alcohol consumption, especially before bedtime
	Stopping smoking
	Adherence to proper sleep hygiene measures
	Weight loss
Devices	Positive airway pressure
	Dental (oral) appliances
	Nasal expiratory positive airway pressure valve
	Body positioning
	Transnasal insufflation
	Tongue retaining
Surgical procedures	Nasal reconstruction
	Uvulopalatopharyngoplasty or uvulopalatal flap
	Genioglossus advancement
	Hyoid advancement
	Maxillomandibular advancement
	Maxillomandibular expansion
	Temperature-controlled radiofrequency tongue base reduction

CPAP treatment should be carefully supervised, usually by sleep medicine specialists working collaboratively with respiratory therapists, to ensure compliance and continued efficacy. Methods of improving compliance with CPAP treatment include use of a variety of mask interfaces, such as oral, intranasal, and full-face masks; use of in-line heated humidification; ramping, wherein pressure is transiently reduced by the patient; use of chin straps to prevent oral air leakage; and use of bilevel positive airway pressure (BiPAP) devices. By independently adjusting pressure levels during respiration, BiPAP devices produce lower pressures during the expiratory phase of respiration, thus permitting the patient to breathe out against a lower positive pressure. Patients experiencing claustrophobic reactions may benefit from desensitization methods and even anxiety-reducing medications (Krakow et al. 2004, 2008). EDS may persist in up to one-third of patients who use CPAP, despite excellent compliance and objectively assessed effectiveness in controlling breathing abnormalities during sleep; hidden causes of persistent EDS should be explored, such as sleep curtailment, comorbid conditions, medication and substance use. If, however, these causes are ruled out, modafinil or armodafinil can be used in conjunction with CPAP to diminish EDS (Physician's Desk Reference 2013).

Oral appliances (Kushida et al. 2006), most of which are mandibular repositioning devices, achieve a forward motion of the mandible and a slight opening of the bite area during sleep. The net effect is an enlargement of the airway. Some also change the posture of the tongue. These are indicated for use in patients with mild to moderate OSAH who prefer them to CPAP therapy or in patients who do not respond to, who are not appropriate candidates for, or who fail treatment attempts with CPAP. Oral appliances are typically fitted by specially trained and qualified dental personnel. Follow-up sleep studies are performed to verify efficacy. Main drawbacks of oral appliances include temporomandibular joint discomfort, dental misalignment, and excessive salivation.

Medications have a limited role in the treatment of OSAH. Supplemental oxygen also has a limited role as a primary treatment. Although it can diminish the severity of oxyhemoglobin desaturation, nocturnal oxygen therapy also can prolong apneas and does not typically decrease EDS (Fletcher and Munafo 1990).

A variety of surgical methods can be used to treat OSAH (Aurora et al. 2010). The most consistently efficacious of these is tracheostomy, which bypasses the entire upper airway. Because of its long-term complications, however, it is not commonly employed. Surgical methods are relied on when other methods are inappropriate, intolerable, or ineffective.

Considerations in Children

Upper airway anatomical abnormalities are greater risk factors in pediatric OSAH patients than in adult OSAH patients. These abnormalities include adenotonsillar hypertrophy, craniofacial anomalies, sinus disease, obesity, and neuromuscular disorders. Therefore, the identification of an underlying cause in a child is necessary prior to management. Although adenotonsillectomy can be effective (Marcus et al. 2012), a portion of children have persistent OSAH postoperatively and may be considered for CPAP management. Behavioral desensitization may be of assistance in adapting to CPAP, especially for those with developmental and behavioral disorders. Weight loss is recommended for overweight children. Intranasal corticosteroids can reduce symptoms in mild OSAH.

Central Sleep Apnea and Sleep-Related Hypoventilation

Diagnostic criteria for central sleep apnea and sleep-related hypoventilation appear in Boxes 36–5 and 36–6, respectively. The extent to which these disorders are encountered in the context of psychiatric practice is unclear. Readers are referred to other sources for a review of treatment modalities (e.g., Barkoukis et al. 2011).

Box 36–5. DSM-5 Diagnostic Criteria for Central Sleep Apnea

A. Evidence by polysomnography of five or more central apneas per hour of sleep.
B. The disorder is not better explained by another current sleep disorder.

Specify whether:

327.21 (G47.31) Idiopathic central sleep apnea: Characterized by repeated episodes of apneas and hypopneas during sleep caused by variability in respiratory effort but without evidence of airway obstruction.

786.04 (R06.3) Cheyne-Stokes breathing: A pattern of periodic crescendo-decrescendo variation in tidal volume that results in central apneas and hypopneas at a frequency of at least five events per hour, accompanied by frequent arousal.

780.57 (G47.37) Central sleep apnea comorbid with opioid use: The pathogenesis of this subtype is attributed to the effects of opioids on the respiratory rhythm generators in the medulla as well as the differential effects on hypoxic versus hypercapnic respiratory drive.

Coding note (for 780.57 [G47.37] code only): When an opioid use disorder is present, first code the opioid use disorder: 305.50 (F11.10) mild opioid use disorder or 304.00 (F11.20) moderate or severe opioid use disorder; then code 780.57 (G47.37) central sleep apnea comorbid with opioid use. When an opioid use disorder is not present (e.g., after a one-time heavy use of the substance), code only 780.57 (G47.37) central sleep apnea comorbid with opioid use.

Note: See the section "Diagnostic Features" in text.

Specify current severity:

Severity of central sleep apnea is graded according to the frequency of the breathing disturbances as well as the extent of associated oxygen desaturation and sleep fragmentation that occur as a consequence of repetitive respiratory disturbances.

Box 36–6. DSM-5 Diagnostic Criteria for Sleep-Related Hypoventilation

A. Polysomnograpy demonstrates episodes of decreased respiration associated with elevated CO_2 levels. (**Note:** In the absence of objective measurement of CO_2, persistent low levels of hemoglobin oxygen saturation unassociated with apneic/hypopneic events may indicate hypoventilation.)

B. The disturbance is not better explained by another current sleep disorder.

Specify whether:

327.24 (G47.34) Idiopathic hypoventilation: This subtype is not attributable to any readily identified condition.

327.25 (G47.35) Congenital central alveolar hypoventilation: This subtype is a rare congenital disorder in which the individual typically presents in the perinatal period with shallow breathing, or cyanosis and apnea during sleep.

327.26 (G47.36) Comorbid sleep-related hypoventilation: This subtype occurs as a consequence of a medical condition, such as a pulmonary disorder (e.g., interstitial lung disease, chronic obstructive pulmonary disease) or a neuromuscular or chest wall disorder (e.g., muscular dystrophies, postpolio syndrome, cervical spinal cord injury, kyphoscoliosis), or medications (e.g., benzodiazepines, opiates). It also occurs with obesity (obesity hypoventilation disorder), where it reflects a combination of increased work of breathing due to reduced chest wall compliance and ventilation-perfusion mismatch and variably reduced ventilatory drive. Such individuals usually are characterized by body mass index of greater than 30 and hypercapnia during wakefulness (with a pCO_2 of greater than 45), without other evidence of hypoventilation.

Specify current severity:

Severity is graded according to the degree of hypoxemia and hypercarbia present during sleep and evidence of end organ impairment due to these abnormalities (e.g., right-sided heart failure). The presence of blood gas abnormalities during wakefulness is an indicator of greater severity.

Circadian Rhythm Sleep-Wake Disorders

DSM-5 diagnostic criteria for circadian rhythm sleep-wake disorders appear in Box 36–7.

Box 36–7. DSM-5 Diagnostic Criteria for Circadian Rhythm Sleep-Wake Disorders

A. A persistent or recurrent pattern of sleep disruption that is primarily due to an alteration of the circadian system or to a misalignment between the endogenous circadian rhythm and the sleep–wake schedule required by an individual's physical environment or social or professional schedule.
B. The sleep disruption leads to excessive sleepiness or insomnia, or both.
C. The sleep disturbance causes clinically significant distress or impairment in social, occupational, and other important areas of functioning.

Coding note: For ICD-9-CM, code **307.45** for all subtypes. For ICD-10-CM, code is based on subtype.

Specify whether:

307.45 (G47.21) Delayed sleep phase type: A pattern of delayed sleep onset and awakening times, with an inability to fall asleep and awaken at a desired or conventionally acceptable earlier time.

Specify if:

Familial: A family history of delayed sleep phase is present.

Specify if:

Overlapping with non-24-hour sleep-wake type: Delayed sleep phase type may overlap with another circadian rhythm sleep-wake disorder, non-24-hour sleep-wake type.

307.45 (G47.22) Advanced sleep phase type: A pattern of advanced sleep onset and awakening times, with an inability to remain awake or asleep until the desired or conventionally acceptable later sleep or wake times.

Specify if:

Familial: A family history of advanced sleep phase is present.

307.45 (G47.23) Irregular sleep-wake type: A temporally disorganized sleep-wake pattern, such that the timing of sleep and wake periods is variable throughout the 24-hour period.

307.45 (G47.24) Non-24-hour sleep-wake type: A pattern of sleep-wake cycles that is not synchronized to the 24-hour environment, with a consistent daily drift (usually to later and later times) of sleep onset and wake times.

307.45 (G47.26) Shift work type: Insomnia during the major sleep period and/or excessive sleepiness (including inadvertent sleep) during the major awake period associated with a shift work schedule (i.e., requiring unconventional work hours).

307.45 (G47.20) Unspecified type

Specify if:

Episodic: Symptoms last at least 1 month but less than 3 months.

Persistent: Symptoms last 3 months or longer.

Recurrent: Two or more episodes occur within the space of 1 year.

Delayed Sleep Phase Type

The delayed sleep phase type of circadian rhythm sleep-wake disorder is more common in children than adults. Chronotherapy, first introduced in 1981 for the treatment of this disorder (Czeisler et al. 1981; Sack et al. 2007a, 2007b), involves a daily 3-hour progressive delay in both bedtime and morning rise time for approximately 1 week until the desired sleep-wake times are achieved. Baseline sleep-wake times are established with self-administered sleep logs; these are also completed daily during therapy. Once the new sleep schedule is achieved, patients are advised to strictly adhere to it and to avoid napping. An opposing strategy, phase-advance chronotherapy, strives to advance sleep-wake patterns through a sequential, daily, 15-minute advance in sleep-wake times. Chronotherapy requires a great deal of patient discipline and planning because it can necessitate scheduling sleep hours during the daytime for a limited period of time, potentially interfering with scheduled social or occupational activities.

Bright light exposure can also be used to advance sleep-wake timing. It is typically administered for 1–2 hours in the morning over a period of weeks or months. The light source can be either natural sunlight or manufactured light boxes providing an illuminance of 2,500–10,000 lux (Cole et al. 2002; Watanabe et al. 1999). During the course of phototherapy, patients are instructed to avoid napping, to adhere to sleep hygiene principles, and to avoid exposure to bright light sources such as television and computer monitors prior to bedtime. Side effects of phototherapy include jumpiness, jitteriness, headache, and nausea. Infrared and ultraviolet light spectra can damage the lens, cornea, retina, and pigment epithelium, and ultraviolet light spectra can interact with photosensitizing agents; these effects can be mitigated by the use of appropriate filters (Chesson et al. 1999; Terman and Terman 1999). Patients with retinopathies, glaucoma, and cataracts should be excluded or carefully evaluated prior to exposure. Hypomania appears to be a rare complication and may be more likely to occur in patients with a history of bipolar disorder (Labbate et al. 1994).

Afternoon or evening melatonin administration can also result in an advance of the sleep-wake cycle. Doses between 0.3 and 5 mg/day have been used. The exact timing and dosage of melatonin therapy, however, have not yet been established (National Institutes of Health 2005). Combining multiple components may enhance the effectiveness of treatment (Weyerbrock et al. 1996).

Therapies for delayed and other types of circadian sleep-wake disorders are summarized in Table 36–11.

Parasomnias

No medications or treatments have FDA approval for the parasomnias, and no methodologically rigorous treatment studies have been reported.

It is generally accepted that genetic factors predispose individuals to the development of non–rapid eye movement (NREM) sleep arousal disorders (sleepwalking and sleep terrors), the diagnostic criteria for which appear in Box 36–8. However, the behavioral abnormalities that are characteristic of these disorders are more likely to occur as a result of the confluence of two additional factors: 1) priming factors, which diminish the threshold for these behaviors—these include, for example, chronic sleep deprivation, a pattern of shift work, and chronic distress or substance use—and

TABLE 36–11. Therapies for circadian rhythm sleep-wake disorders

Delayed sleep phase type	Melatonin before bedtime Bright light in the morning Chronotherapy: sequential delay or advance of bedtimes
Advanced sleep phase type	Bright light in the evening
Irregular sleep-wake type	Remaining active during the day Bright light in the morning Dim and quiet environment in the evening
Non-24-hour sleep-wake type	Melatonin before bedtime Regular sleep-wake times
Shift work type	Planned sleep schedules Dark, noise-free bedroom environment Melatonin 3 mg prior to bedtime Hypnotics at bedtime for insomnia Bright light during night shift Alerting agents (modafinil, armodafinil) prior to work shift Caffeine during work shift Sunglasses during morning commute home

2) precipitating factors, which trigger the event on any given night—these include, among others, acute alcohol or caffeine ingestion, an apneic event in a person who suffers from OSAH, and loud noise during sleep (Pressman 2007). The initial steps in the management of these types of parasomnias, therefore, involve identifying and addressing these factors, as noted in Table 36–12.

Box 36–8. DSM-5 Diagnostic Criteria for Non–Rapid Eye Movement Sleep Arousal Disorders

A. Recurrent episodes of incomplete awakening from sleep, usually occurring during the first third of the major sleep episode, accompanied by either one of the following:
   1. **Sleepwalking:** Repeated episodes of rising from bed during sleep and walking about. While sleepwalking, the individual has a blank, staring face; is relatively unresponsive to the efforts of others to communicate with him or her; and can be awakened only with great difficulty.
   2. **Sleep terrors:** Recurrent episodes of abrupt terror arousals from sleep, usually beginning with a panicky scream. There is intense fear and signs of autonomic arousal, such as mydriasis, tachycardia, rapid breathing, and sweating, during each episode. There is relative unresponsiveness to efforts of others to comfort the individual during the episodes.

B. No or little (e.g., only a single visual scene) dream imagery is recalled.
C. Amnesia for the episodes is present.
D. The episodes cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).
F. Coexisting mental and medical disorders do not explain the episodes of sleepwalking or sleep terrors.

Coding note: For ICD-9-CM, code **307.46** for all subtypes. For ICD-10-CM, code is based on subtype.

Specify whether:

307.46 (F51.3) Sleepwalking type

Specify if:

With sleep-related eating
With sleep-related sexual behavior (sexsomnia)

307.46 (F51.4) Sleep terror type

TABLE 36–12. Treatment strategies for non–rapid eye movement sleep arousal disorders (sleepwalking and sleep terrors)

Goal	Method
Parental reassurance for night terrors	Inform parents that behaviors are not indicative of major disease and are likely to dissipate.
Safety precautions	Remove sharp objects and firearms from bedside. Place mattress on floor. Sleep in first-floor bedroom. Lock doors and windows. For adults, sleep in separate bed from partner. Avoid sleep deprivation. Schedule awakenings prior to usual time of sleepwalking episode occurrence. Take clonazepam 0.25–1 mg at bedtime.
Eliminate triggers	Discontinue caffeine and alcohol. Evaluate for, and treat, sleep disorders that may be triggering behaviors, such as obstructive sleep apnea and periodic limb movements in sleep. Sleep in quiet surroundings. Make sure bed is comfortable. Avoid eating within 4 hours of bedtime.
Diminish priming factors	Normalize sleep-wake schedules. Get adequate amounts of sleep. Avoid exercise within 5 hours of bedtime. Arrange for cool bedroom. Manage anxiety and stress.
Direct treatment in refractory cases	Take clonazepam. Treat with hypnosis. Treat with cognitive-behavioral therapy. Schedule awakenings prior to anticipated events.

Patients with nightmare disorder (see Box 36–9) should closely adhere to sleep hygiene techniques. Recurrent nightmares in children do not always require active management and may subside with reassurance (Kotagal 2012). In adults, nightmares are usually products of underlying disorders, such as posttraumatic stress disorder or personality disorders, and a thorough evaluation for these disorders should be performed, followed by direct management.

Table 36–13 lists treatment strategies for nightmare disorder in children and in adults. In adults, the nightmares generally diminish in frequency and intensity with aging, and conservative measures such as sleep hygiene education may suffice (Schenck and Mahowald 2012).

Box 36–9. DSM-5 Diagnostic Criteria for Nightmare Disorder

307.47 (F51.5)

A. Repeated occurrences of extended, extremely dysphoric, and well-remembered dreams that usually involve efforts to avoid threats to survival, security, or physical integrity and that generally occur during the second half of the major sleep episode.
B. On awakening from the dysphoric dreams, the individual rapidly becomes oriented and alert.
C. The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The nightmare symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).
E. Coexisting mental and medical disorders do not adequately explain the predominant complaint of dysphoric dreams.

Specify if:

During sleep onset

Specify if:

With associated non–sleep disorder, including substance use disorders
With associated other medical condition
With associated other sleep disorder

Coding note: The code 307.47 (F51.5) applies to all three specifiers. Code also the relevant associated mental disorder, medical condition, or other sleep disorder immediately after the code for nightmare disorder in order to indicate the association.

Specify if:

Acute: Duration of period of nightmares is 1 month or less.
Subacute: Duration of period of nightmares is greater than 1 month but less than 6 months.
Persistent: Duration of period of nightmares is 6 months or greater.

Specify current severity:

Severity can be rated by the frequency with which the nightmares occur:

Mild: Less than one episode per week on average.
Moderate: One or more episodes per week but less than nightly.
Severe: Episodes nightly.

Rapid eye movement sleep behavior disorder (Box 36–10) is typically encountered in adults and elderly individuals and has rarely been described in children.

TABLE 36–13. Treatment strategies for nightmare disorder

Children	Write down or draw pictures of the nightmare content.
	Rescript; create more pleasant endings to nightmares.
	Use desensitization techniques.
	Use hypnotherapy.
	Consider pharmacotherapy, which is rarely required, only in refractory cases.
Adults	Treat underlying disorders, such as posttraumatic stress disorder and personality disorders.
	Identify and consider discontinuing or changing doses of offending agents, such as antidepressants, antihypertensives, dopamine receptor agonists, among others. Avoid acute withdrawal from REM-suppressant agents (resulting in REM-rebound nightmares), such as tricyclic antidepressants, clonidine, stimulants, and others.
	Use desensitization techniques.
	Use imagery rehearsal.
	Use rescripting.
	Use pharmacotherapy in refractory cases: cyproheptadine, prazosin, guanfacine, clonidine.

Note. REM=rapid eye movement.

Many of the treatment strategies described for the NREM sleep arousal disorders are useful, including implementing safety measures and addressing triggering and priming factors (see Table 36–12). The diagnostic workup should include a general medical and psychiatric evaluation, with a search for symptoms and signs of OSAH, because the risk of such comorbid conditions, which can have an aggravating influence, increases with aging. In idiopathic cases, clonazepam is the drug of choice, and other medications that have been reported to be of value in anecdotal cases include melatonin, tricyclic antidepressants, and antiepileptic drugs.

Box 36–10. DSM-5 Diagnostic Criteria for Rapid Eye Movement Sleep Behavior Disorder

327.42 (G47.52)

A. Repeated episodes of arousal during sleep associated with vocalization and/or complex motor behaviors.
B. These behaviors arise during rapid eye movement (REM) sleep and therefore usually occur more than 90 minutes after sleep onset, are more frequent during the later portions of the sleep period, and uncommonly occur during daytime naps.
C. Upon awakening from these episodes, the individual is completely awake, alert, and not confused or disoriented.

D. Either of the following:
   1. REM sleep without atonia on polysomnographic recording.
   2. A history suggestive of REM sleep behavior disorder and an established synucleinopathy diagnosis (e.g., Parkinson's disease, multiple system atrophy).

E. The behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (which may include injury to self or the bed partner).

F. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

G. Coexisting mental and medical disorders do not explain the episodes.

Restless Legs Syndrome

The diagnostic criteria for restless legs syndrome (RLS) appear in Box 36–11. RLS should be properly identified prior to treatment, because a variety of medical and psychiatric disorders can mimic its presenting symptoms (see Allen et al. 2003; Rye and Trotti 2012).

Box 36–11. DSM-5 Diagnostic Criteria for Restless Legs Syndrome

333.94 (G25.81)

A. An urge to move the legs, usually accompanied by or in response to uncomfortable and unpleasant sensations in the legs, characterized by all of the following:
   1. The urge to move the legs begins or worsens during periods of rest or inactivity.
   2. The urge to move the legs is partially or totally relieved by movement.
   3. The urge to move the legs is worse in the evening or at night than during the day, or occurs only in the evening or at night.

B. The symptoms in Criterion A occur at least three times per week and have persisted for at least 3 months.

C. The symptoms in Criterion A are accompanied by significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.

D. The symptoms in Criterion A are not attributable to another mental disorder or medical condition (e.g., arthritis, leg edema, peripheral ischemia, leg cramps) and are not better explained by a behavioral condition (e.g., positional discomfort, habitual foot tapping).

E. The symptoms are not attributable to the physiological effects of a drug of abuse or medication (e.g., akathisia).

In psychiatric practice, RLS can mimic drug-induced akathisia, anxiety and agitation, and attention-deficit hyperactivity disorder, among other conditions. Following identification of RLS, a thorough search for secondary causes should be conducted, followed by treatment of the comorbid disorder. Secondary causes include kidney disease, anemia, iron deficiency, depression, pregnancy, gastric malabsorption syndromes, and hepatic disease (Hening et al. 2007). Anecdotal reports suggest that SSRIs and venlafaxine, antipsychotics, and antiemetics can

foment RLS symptoms, whereas other medications such as bupropion may be more protective (Ohayon and Roth 2002; Picchietti and Winkelman 2005). Therefore, whenever possible, these medications should be discontinued or dosages decreased. The workup should also include a ferritin level; even in individuals without evidence of anemia, RLS patients whose ferritin levels are below 50 µg/L may respond to oral ferrous sulfate or gluconate 325 mg/day, with vitamin C 100–200 mg to enhance absorption. These agents do not have FDA indication for this use, however, and may cause gastric irritation and constipation. Ferritin levels should be monitored regularly and iron therapy discontinued once ferritin levels normalize (Sun et al. 1998; Wang et al. 2009).

No formal studies are available that assess the value of behavioral measures. Anecdotal reports suggest the utility of engaging in proper sleep hygiene measures (see Table 36–2); massage; acupuncture; hot or cold baths; distracting activities such as reading, needlework, or video games; scheduling sedentary activities during non-RLS times of the day such as the morning, and scheduling exercise or housework during RLS-prone times such as the afternoon or evening; and delaying sleep times and rise times so that sleep no longer coincides with RLS-prone periods of the night.

Pharmacological agents used for the treatment of RLS are listed in Table 36–14 (Montplaisir et al. 2011). Although gabapentin enacarbil is listed as an antiepileptic agent in the table, its only indication is RLS (Walters et al. 2009). It is an extended-release version of the antiepileptic gabapentin and has almost twice the overall bioavailability. Another agent with extended bioavailability is rotigotine, a dopamine agonist in the form of a transdermal patch (Oertel et al. 2008).

In general, RLS medications should be administered ½ to 1 hour before onset of symptoms, typically in the late afternoon or evening, or at bedtime if symptoms occur following bedtime. Exceptions include gabapentin enacarbil, which is typically administered with the evening meal, and rotigotine, which can be administered anytime during the day, typically after the daily shower. Augmentation is a side effect unique to the dopaminergic agents and generally follows long-term treatment. It is characterized by a worsening of RLS symptoms, progression of symptoms to an earlier time during the day and to other body parts, and a more rapid onset of symptoms while at rest (Garcia-Borreguero et al. 2012). RLS may have an episodic course and may even undergo long-term remission; therefore, episodic reductions in medication dosages may be necessary to ensure that treatment continuation is warranted.

Considerations in Children

There are no FDA-indicated medications for the treatment of RLS in children. Iron supplementation (1.6–7.8 mg/kg/day) was found to be helpful in one series (Mohri et al. 2012). A controlled study of carbidopa-levodopa CR 25/100 mg/day was also shown to be safe and effective (England et al. 2011). The most common side effects were nausea and headache. Pramipexole 0.125–0.5 mg/day and ropinirole 0.25–0.75 mg/day have been recommended by some pediatric sleep experts (Pelayo et al. 2004; Picchietti and Picchietti 2008; Picchietti et al. 2007). Gabapentin 50–300 mg at bedtime has also been described as helpful in alleviating sensory symptoms associated with RLS in children and adolescents (Frenette 2011).

TABLE 36–14. Pharmacological agents for restless legs syndrome (RLS)

Medication	Dosages (mg)	FDA indication for RLS	Side effects	Countermeasures
Dopamine agonists			Nausea and orthostatic hypotension	Lower dose, gradually increase dose
Pramipexole	0.125–0.5	Y	Insomnia	Add hypnotic
Ropinirole	0.5–4	Y	Daytime fatigue and somnolence	Reduce dose or discontinue
Rotigotine transdermal patch	1–3	Y	Compulsive or impulsive behavior	Reduce dose or discontinue
			Tolerance	Take drug holidays
			Morning rebound	Add small daytime dose
			Mild augmentation	Administer medication earlier; consider longer-acting agent; switch classes
			Severe augmentation	Add a small daytime dose, consider longer-acting agent, add or switch to agent of another class, or gradually taper to discontinue
			Application site reaction for transdermal patch	Allow 2 weeks prior to reutilizing the same site
Antiepileptic agents			Somnolence, dizziness	Reduce dose; if significant, discontinue
Gabapentin enacarbil	600 mg with food at 5:00 P.M. (not indicated for epilepsy)	Y		
Gabapentin	100–400	N		

TABLE 36–14. Pharmacological agents for restless legs syndrome (RLS) *(continued)*

Medication	Dosages (mg)	FDA indication for RLS	Side effects	Countermeasures
Dopamine precursors			Same as for dopamine agonists	See countermeasures for dopamine agonists
Levodopa-benserazide	100/25–200/50	N		
Carbidopa-Levodopa	25/100–50/200			
Benzodiazepines			Daytime somnolence	Reduce dose; switch to shorter-acting agent
Clonazepam	0.5–2	N		
Temazepam	15–30	N	Tolerance	Take drug holiday
Nitrazepam	5–10	N		
Opiates			Constipation	Provide symptomatic treatment
Oxycodone	5	N	Dependency	Take drug holiday or withdraw
Propoxyphene	200	N		
Codeine	15–60	N		

Conclusion

Sleep-related symptoms are commonly encountered in psychiatric practice. Although insomnia and daytime somnolence may be related to underlying psychiatric disorders, they may also represent primary disorders or be products of the various sleep disorders described above. Therefore, a systematic evaluation should be conducted to identify comorbid conditions, following which specific management can be provided.

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PART VIII

Sexual Dysfunctions, Paraphilic Disorders, and Gender Dysphoria

Richard Balon, M.D.
Anita H. Clayton, M.D.

Human sexuality used to occupy a very prominent, if not central, place in conceptualizing many psychological and developmental processes. With the arrival of new theories and scientific findings, human sexuality's "place in the sun" gradually diminished. However, an unfortunate parallel process has taken place: human sexuality and the treatment of its disorders seem to be gradually disappearing from psychiatrists' clinical practice. The reason for psychiatry's diminishing interest in clinical sexuality is not exactly clear and is probably multifactorial. Levine (2003) felt that "[m]ental health professionals' interest in these matters [sexual problems] has been thwarted by new biological paradigms for understanding the causes and treatment of mental conditions, the emphasis on short-term psychotherapy, the constriction of insurance support for nonpharmacological interventions, the political conservatism of government funding sources, and the policy to consider sexual problems inconsequential" (p. xiv). Others see a problematic medicalization of human sexuality as the reason for psychiatry's attitudinal change (Cacchioni and Tiefer 2012; Rowland 2007). Pfaus (2008) attributed the cause to the hostile attitude of various agencies to the concept of lifestyle improvement when sexuality is concerned. Interestingly, an area closely related to human sexuality—that of relational problems—has also lacked the attention it deserves in contemporary clinical psychiatry practice (see, e.g., Chambliss and McLeer 2009).

Whatever the reasons are, the results are unfortunate, particularly during a time when sexual medicine is making significant strides and is becoming a true multispecialty discipline, and when there are significant new discoveries in the area of treatment of sexual disorders. It is now

possible to significantly improve our patients' sexual health, and thus their quality of life.

Human sexuality involves an intimate connection of psyche and soma. It has therefore been argued that the area of human sexuality should be an important part of psychosomatic medicine: "Sexual dysfunction, with its complex regulation involving the central nervous system, peripheral nervous system, various hormones, as well as psychological factors including relationship status, and life and circumstances, seems to be a prime example of the interdependence of psychosocial and biologic/physiologic factors" (Balon 2009, p. 69). Various mental disorders and physical illnesses are frequently associated with impaired sexual functioning. Psychotropic and nonpsychotropic medications, as well as substances of abuse, have been associated with sexual difficulties. The negative impact of sexual dysfunction on relationships, marital satisfaction, and overall well-being is also well known. With psychiatry's connection to all of these areas, psychiatrists should be at the forefront of managing patients' sexual problems. They are hopefully still best qualified to address the inseparable and interdependent psychosocial and biological aspects of human sexuality and its impairments.

The new version of psychiatric classification and description of mental disorders, DSM-5, brings changes in the area of classification of sexual disorders and their descriptions and definitions. There are some substantial changes in all areas of classification and description of disorders of human sexuality—sexual dysfunctions, paraphilic disorders, and gender dysphoria. A specific duration is now a required criterion for sexual dysfunctions, and although some disorders (e.g., sexual aversion disorder) were removed, other diagnoses were basically replaced by newly defined diagnostic entities (e.g., dyspareunia and vaginismus by genitopelvic pain/penetration disorder, a simplified combination of their symptomatology). Paraphilias are now called *paraphilic disorders,* and gender identity disorder is now termed *gender dysphoria*. Some of the changes attempt to respond to the question asked by Bancroft (2002) a decade ago: "When is a sexual problem sexual dysfunction?" Others are meant to clarify previous confusions—for example, the distinction between non-normative behavior (paraphilia) and disorder (paraphilic disorder). Not everybody will see all changes as ideal. In addition, there were no field trials to examine the validity and usefulness of the old and new concepts. However, they present a positive, substantial change in most definitions and a significant step forward.

The three chapters in this part—"Sexual Dysfunctions" (Chapter 37) by Richard Balon and Anita Clayton; "Paraphilic Disorders" (Chapter 38) by Lisa Murphy, Paul Fedoroff, and John Bradford; and "Gender Dysphoria" (Chapter 39) by Anne Lawrence—will guide clinicians on how and when to treat as well as what to treat. The authors of these chapters brought together their expertise and clinical wisdom, as well as the latest research developments in the area of management of disorders of sexual functioning, to provide the most up-to-date, practical guide on the treatment of these disorders. Hopefully, these chapters will help rekindle psychiatrists' interest in managing these disorders and ultimately help to improve the quality of life of our patients.

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CHAPTER 37

Sexual Dysfunctions

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Sexual dysfunctions are a heterogeneous group of disorders that are typically characterized by a clinically significant disturbance in a person's level of sexual desire, ability to respond sexually, or experience of sexual pleasure (American Psychiatric Association 2013). DSM-5 includes the following sexual dysfunctions: delayed ejaculation, erectile disorder, female orgasmic disorder, female sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, male hypoactive sexual desire disorder, premature (early) ejaculation, substance/medication-induced sexual dysfunction, other specified sexual dysfunction, and unspecified sexual dysfunction.

DSM-5 has introduced several major changes in the classification of sexual dysfunctions:

1. All of the sexual dysfunctions, except substance/medication-induced sexual dysfunction, now require a minimum duration of approximately 6 months and more precise severity criteria. These requirements were added to make the diagnoses more precise and to distinguish transient sexual difficulties from more persistent sexual dysfunctions.
2. The diagnoses of sexual dysfunctions are no longer necessarily based on the first three phases of the so-called linear sexual response cycle (desire-excitement-orgasm-resolution), because some research suggests that sexual response appears to be a heterogeneous process and that delineation between phases may be difficult for some individuals. Sexual dysfunctions are now gender specific. For women, no separate sexual desire and arousal disorders are delineated in DSM-5; instead, they are combined into female sexual interest/arousal disorder.
3. Dyspareunia and vaginismus are no longer separate diagnoses; instead, they are merged into genito-pelvic pain/penetration disorder. Dyspareunia and vaginismus were considered highly comorbid and not reliably differentiated.
4. There are two groups of subclassifying subtypes: lifelong versus acquired and situational (problems with spe-

cific types of stimulation, situation, or partners) versus generalized. The severity of sexual dysfunction should be indicated by using specifiers rating the distress due to symptomatology in Criterion A as either mild, moderate, or severe.

5. Additional considerations include partner factors; relationship factors; individual vulnerability factors; cultural and/or religious factors; and medical factors related to prognosis, course, and treatment. The specifiers and additional considerations may be useful in planning treatment of sexual dysfunction.
6. Sexual aversion disorder was eliminated from the DSM classification. (In DSM-5, this could be classified as other specified sexual dysfunction.)

The DSM classification deals predominantly with *decreased*—or what is considered to be *negatively impacted/impaired*—sexual functioning. This circumstance is probably related to the difficulties in defining what is "normal" or "average" sexual behavior and lack of research on the range of sexual behaviors in the general population. A high level or increase in sexual desire and activity, in the past called *nymphomania* in women and *satyriasis* in men, is rarely considered dysfunctional (unless it causes severe distress and/or relational problems, or crime) and thus is usually not treated. In addition, increased sexual desire and activity have also been classified as compulsive or addictive behavior and treated as such if deemed necessary. However, not enough data were available to support inclusion of a diagnostic category of hypersexual disorder in DSM-5.

In this chapter, we provide only Criterion A for each sexual dysfunction at the beginning of each treatment section. The remaining criteria are basically the same for most of the sexual dysfunctions:

DSM-5 Diagnostic Criteria B, C, and D for Most Sexual Dysfunctions

B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.
C. The symptoms in Criterion A cause clinically significant distress in the individual.
D. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

General Issues

Several important general issues must be considered before delving into the treatment of each specific sexual dysfunction or disorder:

Overlap of Diagnoses

Sexual dysfunctions, as defined by DSM or the World Health Organization's *International Classification of Diseases,* currently in its tenth revision (ICD-10; World Health Organization 1992), frequently overlap, or may coexist in one individual. A man describing impaired erection may also suffer from hypoactive sexual desire and impaired orgasmic function. Treatment should focus on the primary diagnosis of sexual dysfunction (e.g., erectile disorder) but should also address the other impaired aspects of sexual functioning, and, if they are present, pain disorders (genitopelvic pain penetration disorder) should be addressed first.

Causality

When planning and implementing treatment of sexual dysfunctions, one should keep in mind that the etiology of sexual dysfunctions is usually multifactorial. The causal factors should not be considered only in the frame of the traditional biology-versus-psychology dichotomy. Numerous factors influence sexual behavior, including physiology, psychology, social context, culture, value systems, and other issues that may profoundly affect sexual functioning. If possible, all of these factors should be addressed during diagnosis and treatment. As noted, the more detailed DSM-5 specifiers may serve as guidance for treatment planning.

Differential Diagnosis

A careful differential diagnosis should include organic factors, such as endocrine and cardiovascular disorders (Clayton and Ramamurthy 2008); medications, such as some antidepressants and antihypertensives; and mental disorders, such as major depression and anxiety disorders (e.g., Johannes et al. 2009; Zemishlany and Weizman 2008). Treatment of the underlying cause or disorder (e.g., diabetes mellitus in men with erectile disorder) may or may not alleviate the associated sexual dysfunction.

Multidimensional Perspective

The clinician's view of sexual functioning is frequently limited by the overwhelming complexity of associated factors or attempts to simplify information using a unidimensional perspective. To assist the clinician in organizing information about sexual behaviors and sexual disorders, Peter Fagan (2004, p. 13) has suggested employment of the following four perspectives (as Fagan notes, no single perspective is in itself more valuable than any other):

1. The *disease perspective* turns to physiology, anatomy and medicine and asks what can be learned about the patient's sexual problem from these disciplines. For example, is the low sexual desire caused by abnormally low testosterone?
2. The *dimension perspective* employs the results gained from an evaluation of the individual's personality characteristics and vulnerabilities to assess his or her ability to respond to the conditions resulting from current sexual problems or challenges. For example, is a shy and introverted man plummeted into performance anxiety as he attempts to initiate sex with his partner?
3. The *behavior perspective* helps both the clinician and the patient with a problematic sexual behavior to focus on the behavior rather than collude in addressing more remote issues that are perhaps less anxiety provoking for therapist and patient. Take, for example, the individual who has sexually assaulted children and was himself sexually assaulted as a child. The therapy and life task [are] to control [the patient's] pedophilic urges, not to dwell on the trauma suffered decades ago.
4. The *life-story perspective* states that meaning is important and that sexual behaviors are not universal in their perceived meaning. Meaning-bearing institutions (e.g., religion, academia, developmental psychology, as well as cultural myths gained from anthropology) are important in the life-story perspective as they pertain to sexual expression and behaviors.

We are not necessarily advocating wholesale adoption of Fagan's four perspectives, but these concepts, or a similar organization of information about

the patient and about available interventions, could be very helpful in the treatment of sexual dysfunctions.

Combination of Therapies

Advances in "sexual pharmacology" (Segraves and Balon 2003) have led to the medicalization of sexuality and of the treatment of sexual dysfunction. Frequently, physicians do not consider the multidimensional nature of sexuality and do not pay attention to psychological issues. For instance, phosphodiesterase-5 (PDE-5) inhibitors are prescribed for erectile dysfunction, but psychotherapy or sex therapy is not used. However, as with other psychiatric diagnoses (Perelman 2005), combination therapy may be the most effective therapeutic intervention for any sexual dysfunction. Medications used for treatment of sexual dysfunction should be combined with psychotherapy or sex therapy. This recommendation, however, is based on clinical experience and not on published research, and is limited in practice by the lack of therapists treating sexual disorders.

Continuous Development

The field of treatment of sexual dysfunction has rapidly evolved during the past few decades. As noted, developments in sexual pharmacology have radically changed the landscape of treatment of sexual dysfunction. However, it is important to realize that this landscape will continue to change. (For example, following concerns about blindness in some men treated for erectile dysfunction with PDE-5 inhibitors, a careful review of evidence by Laties [2009] suggests that the risk of blindness is not increased with these medications, but one needs to stay cautious.) Also, additional treatment modalities continue to be approved (e.g., the Eros-CTD [clitoral therapy device], a clitoral vacuum engorgement device approved by the FDA; Billups et al. 2001) that can be incorporated into treatment.

This chapter should serve as guidance or a template for treatment planning, as well as an up-to-date overview of treatments for sexual dysfunctions, and not as a definitive answer to all treatment questions. Some recommendations are based on research studies when these studies are available. Our recommendations regarding the treatment of newly created diagnostic entities (female sexual interest/arousal disorder, genito-pelvic pain penetration disorder) are understandably based on clinical wisdom rather than results of research studies because none have yet been conducted. Given the limited scope of this chapter, many issues (e.g., people not interested in sexuality, sexual "addictions," infidelity) are not addressed here.

Delayed Ejaculation

A. Either of the following symptoms must be experienced on almost all or all occasions (approximately 75%–100%) of partnered sexual activity (in identified situational contexts or, if generalized, in all contexts), and without the individual desiring delay:
   1. Marked delay in ejaculation.
   2. Marked infrequency or absence of ejaculation.

Inability to reach orgasm and/or delayed (or retarded) ejaculation occurs in about 8% of men according to the findings of National Health and Social Life Survey (Laumann et al. 1999). However, the prevalence is probably higher in older age groups and differs across world regions (e.g., it was reported to be 21.1% in

Southeast Asia; Laumann et al. 2005). The etiology of male orgasmic disorder is unknown. Some authors (Waldinger 2005) consider delayed ejaculation to be part of biological variability. Before treatment of this difficult-to-treat disorder is initiated, it is useful to carefully evaluate the patient (e.g., any organic cause such as some antidepressants, psychological reasons such as partner's infidelity), to subtype the disorder (lifelong vs. acquired and situational vs. generalized) (Waldinger 2009). No pharmacological treatment is available for male orgasmic disorder. Various psychological treatment modalities (meditation, relaxation, various psychotherapies), sexual exercises, including masturbation, and vibratory and electrical stimulation have been used with varying degrees of success (level of evidence mostly case reports) (Waldinger 2009).

Retrograde ejaculation (not an inability to reach orgasm, yet a disordered orgasm) could be managed by eliminating possible causative factors (medications), use of pharmacotherapy (ephedrine, imipramine), or surgical bladder reconstruction (Waldinger 2005).

Erectile Disorder

A. At least one of the three following symptoms must be experienced on almost all or all (approximately 75%–100%) occasions of sexual activity (in identified situational contexts or, if generalized, in all contexts):
   1. Marked difficulty in obtaining an erection during sexual activity.
   2. Marked difficulty in maintaining an erection until the completion of sexual activity.
   3. Marked decrease in erectile rigidity.

Erectile disorder (ED) has received much attention during the past 15 years since the introduction of PDE-5 inhibitors (i.e., avanafil, sildenafil, tadalafil, and vardenafil). Estimates of the prevalence of erectile dysfunction in the general population vary. In the National Health and Social Life Survey (Laumann et al. 1999), 10.4% of men reported that they could not keep an erection. The prevalence of ED increases with age and is frequently associated with other diseases (e.g., cardiovascular disease, diabetes mellitus, prostate disease), depression, and factors such as being in a problematic relationship or financial difficulties (e.g., Laumann et al. 2005). As with other sexual problems, the prevalence estimates may vary from culture to culture and across world regions (e.g., prevalence of erectile difficulties was 28.1% in Southeast Asia and 13.3% in Northern Europe in a study by Laumann et al. 2005). However, epidemiological prevalence rates must be viewed with caution, because the DSM-5 criteria are stricter than those used in epidemiological studies.

The management of ED should start with a thorough evaluation. The etiology of ED may be relatively simple (e.g., diabetes mellitus), but this does not imply simple or easy treatment, because ED is usually multifactorial. Based on the evaluation, some contributing factors might be eliminated or modified even before starting treatment. Therefore, a thorough evaluation—as opposed to immediate initiation of treatment with PDE-5 inhibitors or testosterone injections—is indicated.

A possible psychogenic origin of ED should always be considered, especially in younger men. As Fagan (2003) suggests, it is also useful to consider further subtyping of ED, especially in younger males, and to evaluate whether the ED is lifelong versus acquired, is generalized versus situational, or could be due to part-

ner, relationship, or other factors. A careful history should include questions about libido, ejaculatory function (premature vs. delayed ejaculation, anorgasmia), and relationship with the partner, as well as identification of modifiable factors such as alcohol or drug abuse, smoking, and medications (e.g., antihypertensives, some antidepressants), which may induce ED. The sexual history should also incorporate questions about erections during masturbation and on morning awakening. Detailed medical history (Riley and Riley 2009) should include questioning about cardiovascular disease, endocrine disturbances, urogenital disorders and trauma, neurological diseases, spinal trauma, and surgeries. Riley and Riley (2009) also recommend asking about bicycle riding (including stationary bicycles) because this activity could be associated with vascular or nerve damage in the perineal area (Huang et al. 2005). Last but not least, interviewing the partner may also provide important information.

History taking should be followed by a complete physical examination, to include evaluation of secondary sex characteristics, peripheral pulses, bulbocavernosus reflex, penile sensation, and testicular firmness. Finally, laboratory tests should measure serum glucose, serum lipids, and, in men older than 50 years, serum testosterone. Some also suggest evaluating thyroid function.

Riley and Riley (2009) suggest that prior to starting pharmacological treatment of ED, clinicians should consider the following questions:

- Is the ED a symptom of a treatable underlying medical or psychiatric condition?
- Are concomitant medical conditions adequately treated or controlled?
- Is the patient taking any drug(s) that may impair sexual functioning?
- Does the patient have any lifestyle condition that should be addressed?
- Does the patient want treatment for ED?
- Is it safe for the patient to have sexual activity?
- Is it safe to prescribe treatment?
- What is the partner's attitude about the problem and its treatment?
- Does the partner have any medical problems that may impair the partner's ability to participate in pain-free and enjoyable sexual intercourse?
- What are the patient's and partner's expectations of treating ED?

In 1992, the National Institutes of Health issued a consensus statement outlining general considerations in the management of impotence. These considerations remain valid today:

1. Psychotherapy and/or behavioral therapy may be useful for patients with ED without evident organic origin or as an adjunct to medical/urological intervention.
2. Treatment should be individualized to meet the patient's desire and expectations, preferably including both partners in the treatment plan.
3. Although there are several effective therapies, their long-term efficacy is relatively low and there is a high rate of voluntary discontinuation for all forms of ED treatment.

After completing the evaluation, the clinician should provide patient education (Goldstein 1999) focused on the patient's understanding of normal and abnormal erection and the physiology of erection. This should be followed by the elimination of (or an attempt to eliminate) modifiable contributing factors, such as smoking, substance abuse, and obesity (via exercise and/or diet; a Med-

iterranean style diet has been found useful in a study by Esposito et al. [2006]), and the initiation of treatment for any identified underlying disease (e.g., diabetes mellitus). Finally, the pharmacological treatment may be subdivided into first-, second-, and third-line therapies (Goldstein 1999; Wylie 2008).

Wylie (2008) considers oral preparations as first-line treatment; injectable and intraurethral treatments and vacuum constriction devices as second-line treatments; and penile prosthesis and vascular surgery as third-line treatments. Others (e.g., Goldstein 1999) have categorized treatment according to ED etiology and treatment invasiveness or complexity, as follows:

1. First-line treatments (easy to administer, noninvasive, reversible):
   a. Psychotherapy in clearly psychogenic ED
   b. Androgen substitution in hypogonadal men
   c. Oral preparations (e.g., PDE-5 inhibitors, yohimbine)
   d. Vacuum erectile devices and constriction rings
2. Second-line treatments:
   a. Intraurethral preparations
   b. Intracorporeal injectable preparations
3. Third-line treatments:
   a. Surgical approaches (vascular surgery, implantation of penile prosthesis)

Biological Treatment Modalities

Androgen Substitution

Androgen replacement therapy for ED is indicated only in cases of clearly demonstrated hypogonadism and/or low testosterone levels. The results of androgen replacement in ED are frequently not very satisfactory; even in young men with low testosterone levels, improvement during testosterone replacement may be marginal (Althof and Seftel 1995). Administration of testosterone in healthy men with ED is not effective (Schiavi et al. 1997). Androgen replacement in men with hypogonadism is usually lifelong. In the United States, testosterone is available in various preparations: oral (testosterone enanthate, testosterone undecanoate [Andriol]), intramuscular (testosterone undecanoate, testosterone enanthate), mucoadhesive sustained-release buccal (tablets) (Striant), and transdermal (Testim or AndroGel). Many testosterone preparations are available in various over-the-counter forms but have not been properly tested.

Administration of testosterone may be accompanied by various side effects, such as increased prostate size and increased levels of prostate-specific antigen (PSA), gynecomastia, weight gain, acne, hair loss, polycythemia, and reduction of high-density lipoprotein (HDL) cholesterol. Routine monitoring during testosterone replacement should include PSA, serum lipids, and hematocrit. The effect of testosterone on prostate growth (hypertrophy or cancer) has never been proven. Nevertheless, some advocate the use of prostate biopsy prior to testosterone replacement and caution against use of testosterone by men with PSA levels over 3 ng/mL. Monitoring of PSA levels seems to be a prudent practice.

Oral Preparations

Phosphodiesterase-5 inhibitors. Oral preparations—namely, PDE-5 inhibitors—have transformed the treatment of ED. During sexual stimulation, nitric oxide is released from the epithelial and nervous cells, activating guanyl-

ate cyclase, which in turn converts guanosine 5′-triphosphate into 3′,5′ cyclic guanosine monophosphate (cGMP). cGMP relaxes the smooth muscles in the penis, which consequently leads to dilatation of blood vessels, vasocongestion, engorgement, and erection. PDE-5 terminates the action of cGMP. By inhibition of PDE-5, the four available preparations—avanafil (Stendra), sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra)—permit increased and prolonged action of cGMP and thus allow for erection or for longer duration and greater rigidity of erection.

Avanafil, the newest addition to the oral PDE-5 preparations, was found to be effective and safe in the treatment of erectile dysfunction in several studies (e.g., Goldstein et al. 2012; Limin et al. 2010). Because it has a fairly rapid onset of action, avanafil should be taken within 30 minutes of planned sexual activity. The recommended starting dose is 100 mg, which could be either decreased to 50 mg or increased to 200 mg. As is the case for other PDE-5 inhibitors, sexual stimulation is required for response to treatment.

In numerous studies (e.g., Fava et al. 2006; Goldstein et al. 1998; Montorsi et al. 1999), the efficacy of sildenafil has been demonstrated in patients with ED of various etiologies (e.g., idiopathic ED; ED associated with diabetes mellitus, vascular disease, or antidepressant use; ED following radical prostatectomy or spinal cord injury). Sildenafil should be taken approximately 1 hour before sexual activity, because it is effective within 30–60 minutes after oral ingestion (caution: efficacy decreases after a heavy fatty meal). Sildenafil is available in 25-, 50-, and 100-mg pills. The usual starting dose is 50 mg, and this should be lowered or raised on the basis of efficacy and tolerability (e.g., Wylie 2008). The dose should usually not exceed 100 mg. Sildenafil and other PDE-5 inhibitors are absolutely contraindicated with nitrates, because of danger of fatal hypotension. Sildenafil should be used only with extreme caution in patients with unstable angina or coronary artery disease, patients taking multiple antihypertensive agents, and patients with retinitis pigmentosa (sildenafil also inhibits phosphodiesterase-6, an enzyme regulating signal transduction in retinal phosphoreceptors). The usual side effects of sildenafil include headache, flushing, rhinitis, dyspepsia, and transient visual abnormalities. Priapism with sildenafil and other inhibitors of PDE-5 is rare but should be treated as a urological emergency.

Tadalafil also has been shown to be effective in various studies (e.g., Brock et al. 2002; Sáenz de Tejada et al. 2002). The effects of tadalafil start within 30 minutes and last up to 36 hours, a frequently touted advantage requiring no careful planning for intercourse, unlike with sildenafil or vardenafil. The usual dose is 10–20 mg. Side effects and contraindications are similar to those of sildenafil, with the possible exception of a lower incidence of visual abnormalities. Tadalafil was also approved by the U.S. Food and Drug Administration (FDA) for daily use (2.5 or 5 mg) in treating ED and for treatment of benign prostatic hypertrophy (5 mg/day)—a double indication that may be appreciated by older men suffering from both conditions.

The efficacy of vardenafil has also been demonstrated in various studies (Hellstrom et al. 2002, 2003). Vardenafil may begin working within 15 minutes of administration. The usual dose is 5–20 mg. The side effects and contraindications are similar to those of sildenafil and tadalafil.

Several issues should be mentioned in regard to PDE-5 inhibitors. Because no good head-to-head comparison of these medications is available, it is impossible

to know which one is "more efficacious" or "better tolerated." The optimal frequency of usage for greater efficacy and safety is not well established. These drugs may not be covered by insurance companies and can be fairly expensive. They should be preferably used only once a day; multiple dosing has not been explored and could be dangerous (hypotension). Last but not least, the FDA recently issued a warning regarding possible blindness (nonarteritic anterior ischemic optic neuropathy [NAION]) from PDE-5 inhibitors. Patients taking these preparations who experience sudden loss of vision in one or both eyes should seek immediate medical attention. It is important to note that the risk factors for NAION (e.g., hypertension, hypercholesterolemia) are the same as those for ED.

Some have reported relatively high dropout rates from long-term treatment with PDE-5 inhibitors. Psychoeducation, careful monitoring, various therapies (cognitive-behavioral therapy [CBT], sex therapy), and partner involvement should probably accompany any long-term treatment with PDE-5 inhibitors.

Other oral preparations. Apomorphine 2–3 mg sublingually 15–25 minutes prior to sexual activity could improve erection (Heaton et al. 1996; Lal et al. 1987), and the improvement may be dose dependent (Heaton et al. 1996). Apomorphine (Uprima), in contrast to other oral preparations, acts centrally. Yohimbine hydrochloride (Aphrodyne), 5.4 mg up to three times a day, could also improve erection (Guay et al. 2002), although the American Urological Association guidelines state that there is no evidence for its efficacy. Yohimbine has been found useful as an antidote for antidepressant-associated sexual dysfunction (Jacobsen 1992).

Local Preparations

Locally used preparations include intraurethral therapy with alprostadil (medicated urethral system for erection [MUSE]—a semisolid pellet placed into the distal 3 cm of the urethra with an applicator) and intracorporeal injections of papaverine, papaverine plus phentolamine, or prostaglandin E1 (Caverject), or a triple mix of all these substances (for details, see Montorsi et al. 1997; Porst 1997; Segraves and Balon 2003; Werthman and Rajfer 1997).

Mechanical Devices: Vacuum Pumps and Constriction or Compression Rings

The vacuum pump (e.g., ErecAid, Pos-T-Vac) is a rigid tube that is placed over the flaccid, lubricated penis, and a vacuum is created using either a manual or an electric pump (Lewis and Witherington 1997). The negative pressure causes increased inflow into the corpora cavernosa, leading to an erection. A constriction ring is then placed around the base of the penis, thus blocking the venous outflow. The band should be removed after no more than 30 minutes. Compression or constriction rings (e.g., Actis Venous Flow Controller) are used in combination with a vacuum pump or with intracorporeal alprostadil injections or intraurethral suppositories.

Surgical Modalities

Surgical modalities used in the treatment of ED include vascular or microvascular surgery (if angiogram confirms a blockade) and implantation of a penile prosthesis. Implantation of a penile prosthesis is the most expensive and invasive method and should be performed only after all other methods fail.

Psychological Treatment Modalities

The basic components of psychological treatment for ED are psychoeducational, behavioral, cognitive, psychodynamic, and interpersonal. Psychological treatment methods might address the underlying cause (especially in situational ED, acquired or lifelong), the contributory psychological factors, or the psychological consequences of ED. Psychological treatments should also address coexisting mental disorders, such as dysthymia and various anxiety disorders, which may contribute to ED.

The cornerstone of behavioral therapy for ED is *systematic desensitization*, in which exposure to anxiety-provoking situations is combined with relaxation, an intervention originally developed by Masters and Johnson (1970). Cognitive methods are used to modify faulty beliefs and attitudes (Rosen et al. 1994). The psychodynamic approach pioneered by Helen Kaplan (1974), among others, is recommended for men with primary or lifelong ED. At a minimum, psychoeducation should *always* be combined with biological therapies for ED, because high discontinuation rates and frequent requests to switch medication (suggestive of dissatisfaction) were reported in some studies of ED treatments; for example, combining biological therapies with other psychological treatment, such as sex therapy, would be preferable to either alone. As Riley and Riley (2009) note, treatment dissatisfaction may be caused by psychosocial issues, lack of efficacy, and other factors.

Female Orgasmic Disorder

A. Presence of either of the following symptoms and experienced on almost all or all (approximately 75%–100%) occasions of sexual activity (in identified situational contexts or, if generalized, in all contexts):

1. Marked delay in, marked infrequency of, or absence of orgasm.
2. Markedly reduced intensity of orgasmic sensations.

Specify if:

Never experienced an orgasm under any situation.

According to the National Social and Health Life Survey (Laumann et al. 1999), approximately one-quarter of women (24.1%) experience orgasmic problems. This number is comparable to numbers reported in other studies (Meston and Levin 2005). There are cultural and regional differences in prevalence of female orgasmic disorder—the prevalence was found to be two to three times higher in Southeast Asia than in Northern Europe (Laumann et al. 2005). The etiology of female orgasmic disorder is usually multifactorial and includes both underlying psychosocial factors (e.g., age, education, personality, relationship issues, social class) and biological factors (e.g., endocrine disorders, pharmacological agents such as antidepressants).

Careful evaluation, subtyping of orgasmic disorder (lifelong vs. acquired and situational vs. generalized), and determination of specifiers should precede treatment. The first steps in the management of orgasmic dysfunction should be psychoeducation about orgasm itself, and then evaluation of and education about desire and arousal. Next, possible modifiable causes of orgasmic dysfunction should be eliminated (e.g., medication should be changed, substance abuse should be treated). The treatment itself could be divided into biological and psychological treatment modalities.

Biological Treatment Modalities

Numerous pharmacological agents (e.g., bupropion, ephedrine, *Gingko biloba,* sildenafil) have been examined in the treatment of female orgasmic disorder. However, none of them have been found to be superior to placebo. The only possible exception so far has been a nutritional supplement, ArginMax, which contains *Gingko biloba,* damiana leaf (*Turnera aphrodisiaca*), L-arginine, and various vitamins. This supplement was found to increase the frequency of orgasm marginally in comparison with placebo in one small study (Ito et al. 2001). Bupropion has been found to be possibly effective in improving orgasm in women with hypoactive sexual desire disorder (Segraves et al. 2004).

Psychological Treatment Modalities

Psychological treatment modalities are the mainstay of treatment for female orgasmic disorder. Cognitive-behavioral approaches, with a focus on changing attitudes and sexual thoughts, decreasing anxiety, and increasing orgasmic ability and satisfaction (Meston and Levin 2005), employ directed masturbation, sensate focus exercises, and systematic desensitization. Other treatment approaches include anxiety reduction techniques and complex behaviorally based sex therapy/training. Direct masturbation training (LoPiccolo and Lobitz 1972) with sensate focus exercises is the only well-established psychological treatment (Meston and Levin 2005) for female orgasmic disorder. Use of the Eros-CTD (Billups et al. 2001) may be helpful in facilitating orgasm, as suggested by Rellini and Clifton (2011). Bibliotherapy—printed material to provide information and promote change—may also be helpful. Rellini and Clifton (2011) provide a list of books for possible use.

Female Sexual Interest/ Arousal Disorder

A. Lack of, or significantly reduced, sexual interest/arousal, as manifested by at least three of the following:
   1. Absent/reduced interest in sexual activity.
   2. Absent/reduced sexual/erotic thoughts or fantasies.
   3. No/reduced initiation of sexual activity, and typically unreceptive to a partner's attempts to initiate.
   4. Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (approximately 75%–100%) sexual encounters (in identified situational context or, if generalized, in all contexts).
   5. Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (e.g., written, verbal, visual).
   6. Absent/reduced genital and/or nongenital sensations during sexual activity on almost all or all (approximately 75%–100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts).

As noted earlier, FSIAD is a new diagnostic entity in DSM-5, created in response to research suggesting that female sexual response is not necessarily a linear process and to clinical experience that suggests that, at times, delineation between sexual desire and sexual arousal in some women may be difficult. The validity and reliability of this diagnosis have not yet been established yet (no field tri-

als have been conducted); therefore, no literature on prevalence or treatment of this disorder is available. The advice and guidance regarding the management of this disorder are thus inferential and based on evidence of treatment of DSM-IV female hypoactive sexual desire disorder and female sexual arousal disorder (American Psychiatric Association 1994) adapted using clinical wisdom and not based on any clinical trials or other reports.

The prevalence of FSIAD is unknown. The estimates of prevalence for the two previous diagnoses—female hypoactive sexual desire disorder and female sexual arousal disorder—were between 5% and 10% of the U.S. population (Shifren et al. 2008). Results from the Global Study of Sexual Attitudes and Behaviors (Laumann et al. 2005) suggest higher prevalence rates of low sexual desire among women in Southeast Asia, East Asia, and Middle East and of lubrication difficulties in women of Southeast Asia and East Asia. It is difficult to infer too much from these numbers because these epidemiological studies were done using the earlier diagnoses. The diagnosis of FSIAD includes the duration criterion (minimum of approximately 6 months) not used before, which will probably decrease the prevalence estimates of all sexual dysfunctions. Nevertheless, it is also our clinical experience that complaints of low sexual interest (demonstrated in real situations, or by absence of fantasies) and difficulties with arousal are fairly common in clinical practice.

Treatment of FSIAD should start with a thorough evaluation, which needs to be truly biopsychosocial. The evaluation should include a thorough sexual history, a review of systems, a review of medications, a review of lifestyle behaviors, and a general physical examination (possibly including a focused pelvic examination). After consideration of the predisposing, precipitating, and maintaining factors, the clinician should also consider seeing the couple together and separately, because interpersonal factors should be considered first in the treatment process. Seeing the couple separately may shed light on the complex issue of what each partner considers to be adequate sexual stimulation and whether and how each partner's appraisal of the sexual situation differs. The evaluation could also include a psychophysiological assessment suggested by Laan et al. (2005) for female sexual arousal disorder, which could help elucidate whether, with "adequate stimulation by means of audiovisual, cognitive (fantasy), and/or vibrotactile stimuli, a lubrication-swelling response is possible" (p. 135). The use of self-report measures such as the Brief Index of Sexual Function Inventory (Taylor et al. 1994) or the Female Sexual Function Index (Rosen et al. 2000) may also provide some supplementary information. Using the DSM-5 specifiers may also help in treatment planning.

Management should probably start with addressing possible underlying medical and/or mental diseases, particularly depression, which occurred comorbidly in greater than one-third of women endorsing distressing low sexual desire in both a general population (Shifren et al. 2008) and a clinical population (Clayton et al. 2012). Other interventions include providing patient and partner education about sexual functioning, and promoting a healthy lifestyle, such as weight reduction, exercise, smoking cessation, and treatment of possible substance abuse. After addressing these factors and performing a careful differential diagnosis, the clinician needs to decide what treatment modalities to use.

The selection of treatment modalities should be based on prevailing symptomatology using the diagnostic criteria, subtypes and specifiers, and clinical judgment. The selected treatment modalities could be psychological and/or biological, but an astute clinician would implement a combination of both in many situations.

Psychological Treatment Modalities

Potentially helpful therapeutic psychological interventions for FSIAD include sex therapy, sensate focus therapy, CBT, psychodynamic therapy, and couples therapy. Psychological treatment modalities should address any misconceptions about sexuality, examine negative thoughts and attitudes toward sexuality, and seek to improve the couple's nonsexual interactions. Psychological treatments should also address issues such as sexual trauma, body image disruption, stressful life events, partner factors (difference in demands to have sex), cultural factors, and religious orthodoxy. Psychological treatment modalities might also include mindfulness for the arousal dysfunction (Brotto et al. 2008) and education about basic aspects of sexuality for some women and their partners, preferably together.

CBT may be especially useful because women treated with CBT/behavioral therapy frequently report improvement in various aspects of sexual functioning, such as sexual pleasure, sexual satisfaction, perception of sexual arousal, and increased motivation.

Many sex therapists would probably consider using a combination of cognitive therapy (focused on restructuring myths or distorted thinking about sex), mindfulness-based therapy (practice of relaxed wakefulness), behavioral training (e.g., mutual touching, massage), and marital or couples therapy (focused on relational problems, and issues of control, trust, respect, etc.). Clinically, in cases of low sexual desire, marital therapists and individual therapists try to provide the tools for a couple with one partner who has low sexual desire to attain psychological intimacy while identifying and finding a verbal manner of honoring their differences. When intimacy is attained, desire often returns. Although these approaches have not been validated in rigorous studies, they have been successfully used by many clinicians. Further psychological treatment modalities may include masturbatory training (including vibrators), relaxation training, and systematic desensitization.

Biological Treatment Modalities

Cautionary note: Because there are no reports on treatment of FSIAD and no preparation has FDA approval for this indication, the following discussion of treatment is generally theoretical.

Hormones

The use of hormonal therapy has been proposed for the management of various impairments of sexual functioning in women. Although the evidence has been equivocal or weak, use of hormonal therapy has nevertheless been widespread. Because the symptomatology of FSIAD encompasses low sexual desire and impaired arousal, it makes the management of this disorder open to a variety of hormones and their combinations.

Androgens, including testosterone, have been used in women with low sexual desire. Androgen levels in women decline after menopause, and women with decreased androgen levels frequently report low sexual desire. Some data sug-

gest that low dosages of testosterone improve sexual functioning, increase libido, and enhance the overall sense of well-being and vitality. The use of androgens in women poses various risks—namely, masculinizing side effects such as hirsutism, deepening of the voice, acne, and enlargement of the clitoris. Despite these possibilities, topical application of low doses of testosterone gel available for men has been used off-label to treat desire and arousal disorders in women.

Off-label use has increased, as in December 2004 the FDA declined to approve the testosterone patch for women with low sexual desire not because of lack of proven efficacy, but because of questions about potential health risks, specifically cardiovascular, breast, and endometrial effects of testosterone therapy, because there was a lack of safety information for women who used the patch longer than 6 months. However, 4-year open-label extension studies of the testosterone patch in surgically menopausal women showed no important changes in the safety or tolerability profile with long-term use (Nachtigall et al. 2011). Also, the testosterone patch was approved for use in the European Union, and no cardiovascular or cancer signal has been detected. In addition, an interim analysis of a long-term study of testosterone gel in postmenopausal women with hypoactive sexual desire disorder demonstrated no safety signal when compared with placebo (Davis and Braunstein 2012). Clinicians must realize that use of hormones to treat low sexual desire in women 1) is not approved by the FDA and 2) may pose certain risks, especially with long-term use. Therefore, clinicians should always discuss these risks with patients. Most experts would agree that hormonal therapy, if used, should be combined with sex therapy or other psychological modalities.

Systemic administration or replacement of estrogens has been used mainly in postmenopausal or otherwise estrogen-deficient women to alleviate various symptoms associated with menopause, including decreased libido and thinning/atrophy of vaginal mucosa (dryness is usually addressed by using lubricants; see below). The most frequently used agent has been conjugated estrogen (Premarin, in daily doses of 0.3–2.5 mg, with 0.625 mg the most frequently used dose). Estrogens have also been used in combination with androgens. However, good data on the efficacy of systemic hormone administration in female sexual dysfunctions are lacking.

Vaginal estrogen products (creams, Estring) have been approved by the FDA for vaginal atrophy; they may improve mucosal structure, and thus function, resulting in improved genital arousal. Because the effect appears to be predominantly local, vaginal dosing may be particularly helpful in women at risk for complications from systemic estrogen. Topical estrogens should be used routinely and not just prior to coitus, because they address atrophy of mucosa (Al-Baghdadi and Ewies 2009).

Thus, systemic administration of estrogens and/or androgens in women with FSIAD should be implemented with caution, in selected cases, and with informed consent from the patient, which would include consideration of all possible risks. Vaginal estrogens may improve genital arousal without all the complications of systemic estrogens.

Nonhormonal Therapy

Several nonhormonal agents have been used for various sexual dysfunctions in women. There is no solid evidence that PDE-5 inhibitors (avanafil, sildenafil, tadalafil, vardenafil) are effective for low

sexual desire in women, because they do not cross the blood-brain barrier. Bupropion, an antidepressant with dopaminergic and adrenergic properties, might increase desire in nondepressed women with a diagnosis of low sexual desire (Segraves et al. 2004), as well as improve arousal and orgasmic function over baseline. Nevertheless, the evidence is limited, and further studies with bupropion and possibly other dopaminergic agents are needed.

The physiological and biochemical similarities between the clitoris and the penis and the role of vascular congestion in female sexual arousal led to initial enthusiasm about the use of sildenafil in impaired sexual arousal, and early results were encouraging. However, results from several large-scale placebo-controlled studies (e.g., Basson et al. 2002) examining the efficacy of sildenafil in about 3,000 women with impaired sexual arousal were inconclusive, leading Pfizer (the manufacturer of sildenafil) to decide not to file for regulatory approval. There is some evidence that sildenafil improves impaired sexual functioning associated with the use of antidepressants (Nurnberg et al. 2008). Thus, there might be a subgroup of women with impaired arousal who could benefit from sildenafil; however, the clinical characteristics of such a subgroup are not known. As Chivers and Rosen (2010) point out, the lack of efficacy of PDE-5 inhibitors in women is likely attributable to gender differences between physiological and psychological components of sexual response.

Thus, one may try to use either bupropion or a PDE-5 inhibitor in selected cases of FSIAD (although none of these preparations is approved by the FDA), but caution is warranted and thorough informed consent will be required.

Local Preparations

Locally administered preparations that target the lack of lubrication in women include topical estrogens (cream, vaginal rings), topical alprostadil, and over-the-counter lubricants. Although use of these preparations is widespread, evidence from rigorous studies is scarce.

Commercially available lubricants include petroleum-based (e.g., Vaseline, oil), water-based (e.g., K-Y, Astroglide, Sex Grease, Liquid Silk), silicone-based (e.g., Eros Gel, Venus and Eros), and fruit-based (Sylk) preparations; suppositories (e.g., Lubrin); and vaginal moisturizers (e.g., Replens). These products have various advantages and disadvantages. Lubricants should be used prior to coitus (suppositories are administered 45–60 minutes prior to intercourse and may have a more "natural" feel).

A last but not least "biological" and "local" therapy is the Eros-CTD, which is basically a battery-powered clitoral vacuum pump designed to increase blood flow to the clitoris and thus enhance arousal and orgasm. This device was found to enhance arousal, increase lubrication, and improve overall sexual satisfaction (Billups et al. 2001). The Eros-CTD has been approved by the FDA for female sexual arousal disorder and is available by prescription only.

Combined Treatment Approach

A multimodal approach based on prevailing symptomatology and creatively combining psychological, behavioral (e.g., guided masturbation), and biological modalities probably makes the most sense for treating women with FSIAD. Clinicians should consider lubricants and the Eros-CTD as safe treatment options in cases of prevailing impaired arousal symptomatology.

Genito-Pelvic Pain/ Penetration Disorder

A. Persistent or recurrent difficulties with one (or more) of the following:
   1. Vaginal penetration during intercourse.
   2. Marked vulvovaginal or pelvic pain during vaginal intercourse or penetration attempts.
   3. Marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during, or as a result of vaginal penetration.
   4. Marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration.

Genito-pelvic pain/penetration disorder (GPPPD) is a new diagnostic entity in DSM-5 that was created because the DSM-IV sexual pain disorders—dyspareunia and vaginismus—overlapped in their symptomatology and were poorly differentiated. The criteria for GPPPD are fairly simple and straightforward, focusing on pain associated with sexual intercourse and fear or anxiety about pain associated with intercourse. The validity and reliability of this diagnosis have not yet been established (no field trials have been conducted); thus, no literature on this disorder is available. Therefore, the advice and guidance regarding the management of this disorder that we provide in this chapter is inferential and based in clinical wisdom and not on any clinical trials or other reports.

Prevalence of GPPPD is not known. According to the National Health and Social Life Survey (Laumann et al. 1999), the experience of pain during sex is relatively high in younger age groups (e.g., 21% in women ages 18–29 years) and decreases with age (e.g., 8% in women ages 50–59 years). Results from the Global Study of Sexual Attitudes and Behaviors (Laumann et al. 2005) show wide differences in prevalence of pain during sex across various regions and cultures. The prevalence of pain during sex was three times higher among women of East Asia (31.6%) and Southeast Asia (29.2%) than among women in Northern Europe (9%). These are epidemiological estimates using softer criteria (i.e., occasionally, periodically, frequently). Because DSM-5 has introduced a 6-month duration criterion, the prevalence of GPPPD in clinical practice would likely be lower.

As with other sexual dysfunctions, the treatment of GPPPD should start with a thorough multidisciplinary evaluation. The evaluation should first assess the pain's location, quality, intensity (one may use either a Likert-type scale or other scales), trigger, duration, and history. Next is a detailed assessment of sexual functioning, sexual history (e.g., sexual abuse), and relationship history (e.g., avoidance of physical contact, decreased intimacy, interpersonal conflicts). The assessment of sexual functioning and relationship history should also be done, if possible, with the patient's partner. The patient should undergo medical assessment, including a thorough gynecological examination. This should be done by a gynecologist and include a speculum examination, cotton-swab test, internal palpation to locate the pain, vaginal and cervical cultures, and possibly further examinations (hysteroscopy, colposcopy). Some women with GPPPD may need to be evaluated by a pelvic floor physical therapist, dermatologist, and urologist (e.g., to consider cystitis and suspended bladder). Finally, the differential diagnosis of GPPPD should include numerous conditions and illnesses,

such as chronic pelvic pain, Crohn's disease, hemorrhoids, irritable bowel syndrome, neuropathies, sexually transmitted diseases, vaginal atrophy, pelvic organ prolapse, physical trauma, pudendal neuralgia, congenital atrophies, and others.

Treatment

Similar to the assessment, treatment of GPPPD should be multidisciplinary. Psychosocial modalities include CBT (individual and group) and sex therapy (including sexual education, sensate focus, and Kegel exercise). Physical therapies include pelvic floor muscle exercise, pelvic floor rehabilitation, manual therapy techniques, vaginal dilatation, biofeedback, and electrotherapeutic modalities. At times, the physical therapies could be combined.

Various topical, injectable, and systemic medications have been used for different sexual pain disorders. Local anesthetics and botulotoxin (which may decrease pelvic floor hypertonicity) have been frequently used for dyspareunia and other sexual pain complaints in the past; the evidence has been rather weak, however. Systemic medications (tricyclic antidepressants such as amitriptyline, and anticonvulsants such as gabapentin) have also been used with mixed results.

Finally, several surgical procedures (e.g., vestibulectomy that included excision of anterior and posterior vestibular tissue and hymen with vaginal advancement when needed) have been also used in treatment of sexual pain.

The psychiatrist's involvement in the multidisciplinary approach to GPPPD would probably involve a thorough psychiatric evaluation, possibly psychotherapy (CBT), and potentially prescribing systemic medication such as a tricyclic antidepressant.

Male Hypoactive Sexual Desire Disorder

A. Persistently or recurrently deficient (or absent) sexual/erotic thoughts or fantasies and desire for sexual activity. The judgment of deficiency is made by the clinician, taking into account factors that affect sexual functioning, such as age and general and sociocultural contexts of the individual's life.

Low male sexual desire is not rare, endorsed by 15.8% of men in the National Health and Social Life Survey (Laumann et al. 1999). Low sexual desire appears to vary among cultures (12.5% in Northern Europe vs. 28% in Southeast Asia in the Global Study of Sexual Attitudes and Behaviors [Laumann et al. 2005]), and its incidence increases with age. Numerous predisposing, precipitating, and maintaining factors may play a role in the etiology of male hypoactive sexual desire disorder (MHSDD). Examples of such factors include endocrine abnormalities, such as hypogonadism and prolactinemia; other medical illnesses, such as cardiovascular disease, various cancers, and epilepsy; mental illnesses, such as depression or schizophrenia; the effects of numerous prescription medications (Segraves and Balon 2003) and drugs of abuse (Segraves and Balon 2003); the presence of another sexual dysfunction in the patient (e.g., erectile dysfunction) or the partner (e.g., lack of sexual desire, anorgasmia); relationship issues; and various psychosocial issues (e.g., job-related stress, other life events).

The management of MHSDD should start with an evaluation, including a thorough history; meetings with the patient and partner, both together and separately; a physical examination; and, if necessary, laboratory tests (e.g., testoster-

one level in suspected hypogonadism, thyroid-stimulating hormone in suspected hypothyroidism). As with other sexual dysfunctions, promotion of a healthy lifestyle, including weight loss, exercise, smoking cessation, and substance abuse treatment, should be part of the initial intervention.

Specifying whether MHSDD is lifelong or acquired, as well as generalized or situational, is important for planning the clinical management (Maurice 2005). Because there are no good controlled studies of MHSDD treatment modalities, most treatment recommendations are based on clinical reports or expert opinions.

Lifelong generalized MHSDD is unlikely to respond to treatment. Thus, as Maurice (2005) suggested, treatment should focus on helping the patient adapt to the dysfunction (unless he is among the few people who are not interested in sex at all). However, a patient with lifelong generalized MHSDD should still be carefully evaluated, and factors such as physical illness (e.g., endocrine abnormalities) or emotional issues should be ruled out.

Individual psychotherapy and sex therapy are the treatments of choice for lifelong situational MHSDD. Therapy should focus on the situation and the underlying cause. Acquired situational MHSDD, as well as lifelong situational MSHDD, should be treated with individual psychotherapy and sex therapy.

Acquired generalized MHSDD should be carefully explored. Frequently, acquired generalized MHSDD is associated either with another acquired sexual dysfunction (e.g., ED) or with secondary hypogonadism and/or other endocrine abnormalities. It is well known that testosterone production peaks around age 20 years and declines gradually (by 1% a year) after age 40 years. One of the symptoms of secondary hypogonadism is low sexual desire; other symptoms include lower ejaculatory volume, decreased sexual activity, impaired fertility, decreased vigor, fatigue, and dysphoria. The symptoms of hypogonadism, including lower sexual desire, are usually reversible by exogenous testosterone administration (see subsection "Testosterone Replacement" below). One should not forget the possible negative effect of various medications (e.g., serotonergic antidepressants, antipsychotics) on sexual desire; this potential effect should be ruled out prior to further management of MHSDD. Hypothyroidism and hyperprolactinemia can be associated with MHSDD. Restoration of a euthyroid state in cases of hypothyroidism has been accompanied by return of sexual desire. Hyperprolactinemia may be caused by pituitary microadenomas. These tumors may respond to bromocriptine or cabergoline, or may require surgical removal.

Testosterone Replacement

Testosterone replacement is indicated for treatment of hypogonadism at any age (Maurice 2005). Most clinicians would administer testosterone only to men with clearly defined hypogonadism (i.e., men with host of symptoms mentioned in the preceding paragraph and with a testosterone level below normal limits). However, some clinicians also advocate using testosterone replacement for men with testosterone levels in the lower quartile of the normal range or for young males with one or two symptoms (e.g., low sexual desire, lack of vigor). Some argue that because testosterone receptor sensitivity decreases with age, it may not be clear what a "normal" testosterone level is. Nevertheless, clinicians should be cautious about prescribing testosterone in

these situations, given the lack of good long-term data on testosterone use and the fact that "assessment of risks and benefits [has] been limited, and uncertainties remain about the value of this therapy for older men" (Institute of Medicine 2004, cited in Maurice 2005, p. 103).

Transdermal delivery of testosterone, via patch (Androderm Testosterone Transdermal System, administering 1–2 patches to nonscrotal skin daily) or gel (AndroGel, Testim) applied daily, is usually preferred over oral delivery (testosterone enanthate, testosterone undecanoate [Andriol], or mucoadhesive sustained-release buccal tablets [Striant] administered 30 mg bid) or intramuscular injection (e.g., testosterone enanthate [Delatestryl], 50–100 mg weekly or biweekly). Oral androgens are associated with hepatotoxicity. Intramuscular forms could produce supraphysiological levels followed by subnormal levels, whereas the goal is restoration of physiological levels. As discussed earlier in this chapter for erectile disorder, administration of testosterone may be accompanied by various side effects (e.g., prostate enlargement, increased PSA levels, gynecomastia, weight gain, acne, hair loss, polycythemia, reduced high-density lipoprotein cholesterol) and requires monitoring for oversupplementation and changes in laboratory values. Routine monitoring during testosterone replacement should include testosterone level, PSA, serum lipids, and hematocrit. The effect of testosterone in prostate growth (hypertrophy or cancer) has never been proven. Nevertheless, some advocate the use of prostatic biopsy prior to testosterone replacement and caution against use of testosterone in men with PSA levels >3.0 ng/mL. One should always remember that the goal of testosterone replacement is restoration of testosterone levels to a mid-normal range level; no high levels of testosterone are desirable or recommended.

Premature (Early) Ejaculation

A. A persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 minute following vaginal penetration and before the individual wishes it. (Note: Although the diagnosis of premature [early] ejaculation may be applied to individuals engaged in nonvaginal sexual activities, specific duration criteria have not been established for these activities.)

Criterion B, in addition to the 6-month duration requirement, also specifies that the symptoms in Criterion A

must be experienced on almost all or all (approximately 75%–100%) occasions of sexual activity (in identified situational contexts or, if generalized, in all contexts).

Premature (early) ejaculation (PE) is considered to be the most prevalent male sexual dysfunction. Estimates of its prevalence vary from 21% in the National Health and Social Life Survey (Laumann et al. 1999) to 40% or even 75% in other studies (Althof 1995; Metz et al. 1997). However, most experts would agree that the prevalence is about 20%–30%. Although prevalence seems to vary across world regions, the differences are smaller than in cases of other sexual dysfunctions (Northern Europe 20.7%, Middle East 12.4%, Southeast Asia 30.5%, [Laumann et al. 2005]). Age, novelty of the sexual partner or situation, and recent frequency of sexual activity should be taken into account when making the diagnosis of PE. Further criteria and subclassifications are similar to those of the other sexual dys-

functions. Waldinger (2008) has proposed a new classification of PE, which would include lifelong PE, acquired PE, natural variable PE, and premature-like ejaculatory dysfunction. Little is known about the etiology and physiology of ejaculation and premature ejaculation; however, serotonergic activation plays an important role in orgasmic inhibition (e.g., Segraves 1989), and serotonergic drugs have been used successfully in the treatment of PE.

Biological Treatment Modalities

Serotonergic antidepressants such as fluoxetine, paroxetine, sertraline, and clomipramine have been found useful as off-label treatments of PE (Balon 1996; Waldinger 2005). These agents may be used either daily (fluoxetine 20–40 mg/day; clomipramine 25–50 mg/day; paroxetine 20–40 mg/day; sertraline 50–200 mg/day) or on demand (e.g., clomipramine 10–50 mg 4–6 hours prior to intercourse; topical anesthetics; selective serotonin reuptake inhibitors; tramadol). The administration of serotonergic antidepressants to men with PE has also been found to improve sexual functioning in their partners (Althof et al. 1995). The side effects of these drugs are usually minimal. It is important to point out that no medication has FDA approval for the treatment of PE. The serotonergic medication dapoxetine (marketed as Priligy, Kutub, or Duratia outside the United States) has been found useful in the treatment of PE (30, 60, or 90 mg on demand), yet has not been approved by the FDA. Because it is widely available through the Internet, physicians should be aware of its use. There is no solid evidence for on-demand usefulness of PDE-5 inhibitors for treatment of PE.

Anesthetic ointments, applied locally on demand (e.g., SS Cream [Choi et al. 1999], prilocaine-lidocaine cream), have also been found useful in the treatment of PE.

Psychological Treatment Modalities

The Semans pause maneuver (Semans 1956), the Masters and Johnson pause-squeeze technique (Masters and Johnson 1970), and the Kaplan stop-start method (Kaplan 1989) have long been standard therapeutic techniques for the treatment of PE. The core feature of the Semans pause maneuver is that when the man starts to feel sensations indicative of upcoming ejaculation, he asks the partner to stop the stimulation immediately. Once the sensation of upcoming ejaculation disappears, the stimulation is reintroduced. This cycle is repeated till the man is able to postpone ejaculation indefinitely. In the pause-squeeze technique, the partner squeezes firmly the glans penis to reduce tumescence in addition to cessation of movements during sexual activity when the patient feels sensations indicative of upcoming ejaculation. This "cycle" is again repeated. As Waldinger (2009) pointed out, although these techniques are widely promoted and used, their efficacy has not been adequately studied.

Other therapies, such as cognitive therapy, psychodynamic therapy, education, and muscle relaxation, have also been used in treating PE.

Psychotherapies, which are used mainly to address coping with PE (Waldinger 2005), should probably always be combined with medication in the treatment of PE. Combination treatment—use of standard behavioral methods (e.g., stop-start) in conjunction with medication—should probably be reserved for treatment-resistant cases. Medication and behavioral techniques should probably be

used indefinitely, because discontinuation of treatment usually leads to relapse. However, good long-term treatment studies of PE treatment are not available.

Substance/Medication-Induced Sexual Dysfunction

The DSM-5 criteria for substance/medication-induced sexual dysfunction differ from the criteria for the other sexual dysfunctions:

A. A clinically significant disturbance in sexual function is predominant in the clinical picture.

B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

   1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication.
   2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by a sexual dysfunction that is not substance/medication-induced. Such evidence of an independent sexual dysfunction could include the following:

   The symptoms precede the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the evidence of an independent non-substance/medication-induced sexual dysfunction (e.g., a history of recurrent non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

The 6-month duration criterion clearly does not apply in this diagnosis.

The first step in the treatment of substance/medication-induced sexual dysfunction involves the discontinuation, if possible, of the offending agent. If the dysfunction persists or if it is not feasible or possible to discontinue the medication (e.g., because chronic resistant depression responds to one specific antidepressant, or because hypertension responds to one specific antihypertensive agent), the clinician should treat the specific sexual dysfunction (e.g., ED) either by using numerous "antidotes" (for details, see Segraves and Balon 2003) or according to the guidance provided in this chapter for specific sexual dysfunctions.

Conclusion

There have been major developments in the treatment of sexual dysfunctions, namely in the area of sexual pharmacology, during the past two and a half decades. However, the complexity of sexual functioning, the less than full understanding of human sexuality, the recently reported complications associated with some of the drugs used and proposed for the treatment of sexual dysfunction, and the complicated intertwining of psychology and physiology underscore that creativity and caution, or cautious creativity, should be the rule in the treatment of these disorders. Treatment of sexual dysfunctions should be individualized, based on a biopsychosocial approach, and combine various treatment modalities (Perelman 2005). Organizational schemes, such as the "perspectives approach" outlined by Fagan (2004) or the detailed use of specifiers and sub-

types, may be useful in devising a treatment plan.

Psychological treatment modalities—namely, various forms of CBT and sex therapy with added focus on attaining psychological intimacy—continue to play an important and at times dominant role in the treatment of sexual dysfunctions.

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CHAPTER 38

Paraphilias and Paraphilic Disorders

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In this chapter, we review current treatments and the treatment efficacy for a variety of paraphilic disorders. Although most pronouns in this chapter are masculine, the advice in this chapter applies equally to male and female patients, aside from the section on antiandrogens.

This chapter focuses on treatment of adults. Treatment of adolescents, children, and special groups, such as individuals with intellectual disabilities, developmental delays, head injury, dementia, and significant major mental illnesses, is not described in detail. Although the general treatment principles remain the same for these special groups, we recommend that readers consult more specialized sources.

One shortcoming of treatment studies, primarily studies on pharmacological treatments, is the limited ability to ensure and control for treatment compliance. The references cited in this chapter, unless otherwise noted, did not specify the methods used to monitor adherence to oral pharmacotherapy.

This chapter is concerned primarily with treatments for persons who have unconventional sexual interests and/or behaviors that have caused harm to themselves or others. It is not intended to advocate for one treatment method over another. In fact, if there is one common theme that emerges from a review of treatments over the last 100 years, it is that a combination of treatment paradigms is more effective than a single approach or treatment algorithm applied dogmatically. What works well for one person may not work at all for another. It is important to individualize treatment, to reevaluate the efficacy of the treatment often, to be willing to switch paradigms, and most importantly to convey realistic optimism about prognosis.

In DSM-5, a distinction is made between paraphilias and paraphilic disor-

ders (American Psychiatric Association 2013). *Paraphilias* per se do not cause harm or distress. In contrast, *paraphilic disorders* are diagnosed if they cause personal harm and/or distress to self or others. DSM-5 therefore acknowledges the distinction between sexual interests and behaviors that cause clinical concern and those that are simply unconventional. The DSM-5 diagnostic criteria for paraphilic disorders are presented later in the context of the specific disorders.

Overview of Current Treatment Approaches

Cognitive-Behavioral Therapies

Cognitive-behavioral therapy (CBT) for paraphilias gained momentum during the 1980s and is still one of the most popular treatment approaches for these conditions. The goal of CBT for persons with paraphilias is to increase their control over problematic sexual interests and acts and to equip them with the skills and attitudes necessary to achieve their goals in healthy and prosocial ways (Fedoroff and Marshall 2010). CBT is often used in combination with other treatments. A meta-analysis by Hanson et al. (2002) examined the use of nonpharmacological treatments of men with paraphilias and found that 63% of treatment providers used some form of CBT. CBT for persons with paraphilias addresses aims to enhance voluntary control over sexual interests and behaviors by altering thought patterns and perceptions. The cognitive distortions of one person with a specific paraphilia may be different from another, even if they share the same paraphilia (Fedoroff 2008, 2010).

Cognitive restructuring, a key component in CBT, occurs in a three-step process: 1) identify the sexual thoughts and cognitive distortions that precede deviant behaviors, 2) identify and alter thought patterns leading to potentially high-risk situations, and 3) use interventions that substitute more prosocial and adaptive thoughts for the deviant sexual thoughts (Fedoroff 2008, 2010; Fedoroff and Marshall 2010). Cognitive restructuring involves therapeutic discussion (often in group therapy sessions) about beliefs pertaining to sexual interest and, in cases of illegal paraphilias, false justifications for offending. A group therapy format permits discussion about why different thought patterns are distorted or illogical. Issues relating to victim empathy can also be addressed in a similar manner (Fedoroff and Marshall 2010; Marshall et al. 2006, 2008a).

Relapse Prevention

Frequently, CBT is used jointly with relapse prevention (RP) techniques to treat paraphilic disorders. Based on treatments for addictive behaviors, RP evolved to include treatment of sexual offenders and persons with paraphilic disorders (Laws and Ward 2006). One of the organizational principles of RP is the identification of behavioral chains and triggers. The goal of RP is to assist the patient in identifying, anticipating, and coping with triggers that may lead to a potential relapse or re-offense. Cognitive, behavioral, educational, and skill developing measures are also used in this approach (Laws and Ward 2006).

Within RP, the process requires that the patient understand that relapse or re-offense can occur due to multiple decisions made prior to the offense. The patient, in individual or group therapy, is asked to identify potential triggers and to anticipate high-risk situations and the strategies that can be used to avoid or es-

cape the situation (Fedoroff 2008, 2010; Fedoroff and Marshall 2010; Laws and Ward 2006). For example, a man with pedophilia may put himself in a high-risk situation if he spends time alone with a child. The alternative is to make an active decision not to be alone with children.

The focus in RP therapy is on both emotional and external warning signs of potential relapse. This may include difficulty sleeping, eating, or socializing. Patients are assisted to develop a well-defined offense chain, which can be translated into a series of behavioral and cognitive indicators (Fedoroff 2008; Fedoroff and Marshall 2010; Laws and Ward 2006). Similar to CBT, insight into personal relapse cycles and triggers can be used to evaluate the rationalizations used to justify risky behaviors. The goal is for patients to recognize their relapse behavioral patterns early in their cycle so they can interrupt the sequence of increasingly risky behaviors (Marshall et al. 2006, 2008a).

Good Lives Model

Emerging from criticisms of RP, which focuses on avoidance, the Good Lives Model (GLM) is based on ways to maximally fulfill human potential and individual strengths rather than focusing on psychological deficits. GLM is rooted within a strength-based framework that takes an individualized rehabilitative approach to interests, abilities, and aspirations. It emphasizes that happiness and well-being do not come solely from extrinsic factors, such as the attainment of wealth and goods (see www.goodlivesmodel.com) (Ward and Stewart 2003). According to the model, all human beings seek happiness through intrinsic goals that attempt to satisfy nine basic human needs (known as "goods"): healthy living, knowledge, excellence in work and play, excellence in agency, inner peace, relatedness, spirituality, happiness, and creativity (Marshall et al. 2006; Ward and Stewart 2003).

Concerning paraphilias, the model suggests that persons with paraphilic disorders exhibit deviant sexual interests or behaviors because they lack the internal and external resources necessary to satisfy sexual needs in less harmful ways (Ward and Stewart 2003). According to GLM, people can fulfill primary goods through sexual relations. Examples include healthy living through physical satisfaction, relatedness through intimacy, and inner peace through emotional regulation (Marshall et al. 2006). In contrast, individuals with pedophilia may seek out intimate relationships and emotional regulation with children because they feel inadequate when pursuing consensual adult sexual relationships.

GLM seeks to identify obstacles preventing individuals from having a fulfilling life and helps them develop the skills, beliefs, and supports necessary to meet their needs without causing harm (Marshall et al. 2006). GLM therapy identifies areas of need while providing the patient with tools useful to live in a more fulfilling, prosocial, and law-abiding manner (Ward and Stewart 2003). Typically, the GLM treatment approach is used in combination with RP.

Pharmacological Approaches

WFSBP Guidelines for Biological Treatment

In 2010, the World Federation of Societies of Biological Psychiatry (WFSBP) released a comprehensive review of pharmacological agents used in the treatment of

paraphilias. Based on a meta-analysis of peer-reviewed empirical studies published between 1969 and 2009, the document proposes a set of guidelines for the treatment and management of paraphilias, focusing primarily on adult males. It includes a treatment algorithm based on published studies (see Table 38–1 for a summary of the algorithm).

Selective Serotonin Reuptake Inhibitors

The first use of a serotonergic medication involved a case report of the successful treatment of a 46-year-old man with transvestic fetishism with buspirone. Treatment efficacy was measured in an ABA design based on self-report and the report of his wife, who noted an increase in his sexual interest in her instead of her clothes (Fedoroff 1988). Kafka and Prentky (1992) studied a group of 16 adult men in an open trial of the effects of fluoxetine on men with paraphilia(s) and men with self-reported "hypersexuality." Over a 3-month period, using an average dosage of 40 mg/day of fluoxetine, all patients reported overall improved sexual functioning. The authors hypothesized that fluoxetine reduced both paraphilic and hypersexual behaviors while still permitting normal sexual arousal. An uncontrolled retrospective study of 16 adult men with paraphilias undergoing psychotherapy and treated with selective serotonin reuptake inhibitors (SSRIs) reported a marked reduction of paraphilic symptoms (Krauss et al. 2006). A retrospective study on the impact of three different SSRIs (fluvoxamine, fluoxetine, and sertraline) on paraphilic fantasies, urges, and behaviors found all three medications to be equally effective. Treatment effect was measured through the Clinical Global Impressions Scale and self-reports of frequency and severity of deviant sexual fantasies (Greenberg et al. 1996).

Consideration has also been given to paraphilias being part of the obsessive-compulsive disorder (OCD) spectrum. The use of SSRIs has been reported in individuals with paraphilias and comorbid OCD, impulse-control disorders, and depressive disorders. Rösler and Witztum (2000) have suggested that SSRIs may be ideally effective only in men that have a true OCD component to their sexual interest and behaviors.

Although lower dosages of SSRIs have been shown to decrease paraphilic sexual interest and arousal in some persons, higher dosages are associated with acquired inability to reach orgasm. Some men have reported returning to paraphilic fantasies and behaviors when they are unable to attain orgasm through conventional fantasies and behaviors. Therefore, lower dosages of SSRI may be more effective in the treatment of paraphilic disorders (Fedoroff 2008, 2010).

There is no evidence that any specific SSRI medication has superior efficacy over another SSRI in the treatment of paraphilic disorders. SSRIs are less effective than antiandrogen medications for the purpose of reducing sex drive. When using an SSRI to treat a paraphilic disorder, clinicians should prescribe the lowest dose used to treat mood disorders and increase the dose gradually to avoid inducing inhibited orgasm, because this may encourage a return to paraphilic activities.

Testosterone-Reducing Agents

Testosterone-reducing agents have been identified as the gold standard in treating paraphilic disorders when overall reduced sex drive is desired as part of the treatment plan (Thibaut et al. 2010). Testosterone plays a role in the regulation of

TABLE 38–1. Summary of World Federation of Societies of Biological Psychiatry risk treatment algorithm for paraphilias

Risk level	Goals	Actions
1	Manage low-risk paraphilic fantasies and behaviors. Have no impact on conventional sexual fantasies and behaviors.	No medication. Use of psychotherapy (ideally, cognitive-behavioral therapy).
2	Manage "hands-off" paraphilias with low risk of sexual violence. Have minor impact on conventional sexual fantasies and behaviors.	If no results with level 1, use low-dose SSRI (start at dose for mood disorders).
3	Manage "hands-on" paraphilias (those without penetration). Aim for moderate reduction of conventional sexual fantasies and behaviors.	If no improvement with SSRIs over 4- to 6-week period at high dose, maintain SSRI and add low-dose antiandrogen (CPA or MPA 50–100 mg/day).
4	Manage moderate to high risk of sexual violence (more intrusive fondling; limited victims; no sadistic sexual fantasies or behaviors). Aim for substantial reduction of all sexual fantasies and behaviors.	If no improvement with level 3 treatment, use CPA 200–330 mg/day or MPA 50–300 mg/day. Use intramuscularly for noncompliant patients. Maintain SSRI use if paraphilia is comorbid with anxiety, depression, or obsessive-compulsive symptoms.
5	Control severe paraphilias with high risk of sexual violence (sadistic sexual fantasies or behaviors present; physical violence). Aim for almost complete suppression of all sexual fantasies and behaviors.	If no results at level 4 or patient is noncompliant, add GnRH agonist (triptorelin or leuprolide 11.25 mg im every 3 months). For first month maintain CPA or MPA to prevent flare-up effect.
6	Control most severe "catastrophic" paraphilic cases. Aim for complete suppression of all sexual desires and behaviors.	If no results at level 5, maintain use of GnRH agonist as in level 5 and add CPA 200–400 mg im weekly or MPA 300–500 mg im weekly.

Note. CPA = cyproterone acetate; GnRH = gonadotropin releasing hormone; MPA = medroxyprogesterone acetate; SSRI = selective serotonin reuptake inhibitor.
Source. Adapted from Thibaut et al. 2010.

sexual desire, fantasy, aggression, and cognition. There is no evidence that people with paraphilic disorders have above-average levels of testosterone. However, suppression of sexual arousal can assist patients to focus on aspects of treatment designed to correct previous social skill deficits (Fedoroff 2008, 2010). Sometimes referred to as "chemical castration," antiandrogens provide a pharmacological alternative to the infrequent approach of surgical castration. Currently, there are two main types of testosterone-reducing medications: antiandrogens and gonadotropin-releasing hormone (GnRH) partial agonists (Fedoroff 2008, 2010; Thibaut et al. 2010).

Antiandrogens

Medroxyprogesterone acetate. Medroxyprogesterone acetate (MPA) is a steroidal progestin (variant of progesterone). In males, MPA at higher dosages can effectively decrease testosterone levels by the inhibition of luteinizing hormone secretion, causing down-regulation of testosterone production (Fedoroff 2008, 2010; Maletzky 2002). MPA is available in both oral (po) and intramuscular (im) formulations. Typical dosages for men are 50–400 mg/day po or 300 mg im weekly (Fedoroff 2008; Maletzky 2002). MPA has reliable effects on sexual functioning (i.e., reductions in sex drive, deviant sexual fantasies, and sexual activity) (Fedoroff 2008, 2010; Thibaut et al. 2010).

Since early reports of MPA in the successful treatment of men with paraphilias, MPA has become the most frequently used medication for the reduction of sex drive within the United States (Thibaut et al. 2010). In an open nonblind trial involving seven patients, Gottesman and Schubert (1993) described complete elimination of deviant sexual behaviors in patients with paraphilias treated with MPA at a dosage as low as 60 mg/day. Testosterone levels and self-reports of paraphilic fantasies were used to measure change.

Recommendations from the WFSBP guidelines note that MPA should be used with caution because of potential physical and emotional side effects. MPA should only be prescribed to persons who can provide informed, voluntary, and reversible consent. Generally, MPA is not prescribed to treat paraphilic disorders in children who have not reached puberty and therefore have not completed maturity, including fusion of their bone epiphyses. Compliance can be checked by monitoring serum free testosterone levels. Patients should be monitored for osteoporosis and may benefit from a baseline bone densitometry with subsequent scans every 2–3 years. Other common side effects include weight gain, diabetes, and hot flashes (Thibaut et al. 2010).

Cyproterone acetate. Cyproterone acetate (CPA) is an antiandrogen that is not available in the United States but is popular in Canada and throughout Europe. Oral CPA can be prescribed at a dosage of 50–300 mg/day. The typical starting oral dosage for both CPA and MPA is 100 mg/day, and intramuscular injections can be given at 200–400 mg once every 2 weeks. CPA dosage can be titrated either to completely suppress sex drive or to moderately reduce sex drive while preserving the ability to obtain erections in noncriminal sexual situations (Thibaut et al. 2010).

Positive results were noted in a review of 10 studies on the efficacy of CPA in 900 paraphilic male subjects. In the sample, approximately 20% were men with pedophilia. Within a 4- to 12-week period, 80%–90% of the men showed a decrease in paraphilic sexual fantasy and behav-

iors (Thibaut et al. 2010). A prospective, double-blind, crossover study of CPA used in men with paraphilias showed a statistically significant decrease in deviant sexual activity for the CPA group when compared with placebo and no-treatment comparison groups. Assessment of changes was based on a hormone profile, penile tumescence, and self-report (Bradford and Pawlak 1993a).

The following should be checked prior to CPA treatment and monitored during treatment: free testosterone, luteinizing hormone, follicle-stimulating hormone, prolactin, and glucose levels; blood cell count; kidney and liver functioning; and bone density. Similar to MPA, CPA should not be used in patients who cannot provide informed, voluntary, and reversible consent, or in young people prior to completion of puberty and bone growth. These medications should be used with caution in patients with hepatocellular disease, liver carcinoma, diabetes mellitus, severe hypertension, thromboembolic disease, cardiac or adrenal disease, depression, tuberculosis, epilepsy, or psychosis (Thibaut et al. 2010). The WFSBP guidelines noted concern about compliance rates for oral CPA. Compliance can be monitored via free testosterone serum levels. Many men find that partial suppression of their sex drive is sufficient. Others prefer to take the medication only during times of increased risk, such as during the summer months for exhibitionists. Potential adverse side effects include gynecomastia, weight gain, diabetes, and osteoporosis. These medications should not be relied upon as contraceptives for men.

Gonadotropin-Releasing Hormone Agonists

GnRH analogues have been used primarily in the treatment of testosterone-dependent cancers and precocious puberty. There are now at least seven commercially available GnRH agonists. The most commonly studied GnRH agonists used in the treatment of paraphilic disorders are triptorelin and leuprolide. These GnRH analogues result in the reduction of luteinizing hormone and testosterone to castration levels within a 2- to 4-week period (Thibaut et al. 2010). Both triptorelin and leuprolide are available only in long-acting formulations, permitting intramuscular injections either monthly, every 3 months, or less frequently (Fedoroff 2008; Thibaut et al. 2010).

A review of published treatment studies using triptorelin to treat men with paraphilic disorders included a total of 75 male participants. The average dose was 3.85 mg/month im for a duration of months up to 7 years. No deviant sexual fantasies or behaviors were reported, but there was one re-offense. The maximum effect of a sharp reduction in deviant sexual fantasies or behaviors occurs within a 1- to 3-month period (Thibaut et al. 2010). One case study of a hospitalized male sex offender over a 54-month period compared treatment using placebo, CPA, and leuprolide (Cooper and Cernovsky 1994). The authors noted that for this man, leuprolide suppressed almost all deviant arousal, as measured by phallometry and self-report.

The WFSBP guidelines identify GnRH treatments as being very efficacious even in patients who failed to respond to other treatment modalities (i.e., psychotherapy or antiandrogens). Osteodensitometry should be completed prior to starting the medication and every 2–3 years while the medication is being taken. Calcium and vitamin D supplements are also recommended. Although the adverse effects of GnRH are generally reversible, these medications should be prescribed only with informed voluntary consent. GnRH treatment was noted as the most promising

pharmacological treatment for men with paraphilias involving a high risk of sexual violence (Thibaut et al. 2010). However, as with all pharmacological treatments, GnRH medications are only one part of an effective treatment plan for men with paraphilic disorders. Currently, they are available only in injectable forms.

Patients often report fewer side effects with GnRH medications than with antiandrogens, and GnRH medications are often effective even when trials with antiandrogens or SSRIs have failed. When presented with the risks and benefits of SSRIs, antiandrogens, and GnRH medications, many men choose GnRH medications, especially when they learn that the sex drive reduction is reversible when they stop taking the medication.

Paraphilias Associated With Criminal Activity

Exhibitionistic Disorder

Overview

Exhibitionism comprises approximately one-third of documented sexual offenses (see Box 38–1). Exhibitionism and voyeurism have the highest rates of sexual recidivism of all the paraphilias associated with criminal activity. Exhibitionism co-occurs with voyeurism approximately 80% of the time and with frotteurism approximately 70% of the time (Aggrawal 2009; Morin and Levenson 2008).

Box 38–1. DSM-5 Diagnostic Criteria for Exhibitionistic Disorder

302.4 (F65.2)

A. Over a period of at least 6 months, recurrent and intense sexual arousal from the exposure of one's genitals to an unsuspecting person, as manifested by fantasies, urges, or behaviors.

B. The individual has acted on these sexual urges with a nonconsenting person, or the sexual urges or fantasies cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify whether:

Sexually aroused by exposing genitals to prepubertal children
Sexually aroused by exposing genitals to physically mature individuals
Sexually aroused by exposing genitals to prepubertal children and to physically mature individuals

Specify if:

In a controlled environment: This specifier is primarily applicable to individuals living in institutional or other settings where opportunities to expose one's genitals are restricted.
In full remission: The individual has not acted on the urges with a nonconsenting person, and there has been no distress or impairment in social, occupational, or other areas of functioning, for at least 5 years while in an uncontrolled environment.

Treatment

Treatment of DSM-5 exhibitionistic disorder has traditionally relied on medications and group therapies using CBT and RP techniques. A survey of clinicians involved in the treatment of exhibitionism indicated that 92% of clinicians use cognitive restructuring, 94% use techniques of RP, and 75% include victim empathy training. Social skills and interpersonal intimacy were also used (89% and 83%, respectively) (Morin and Levenson 2008).

A meta-analysis on the efficacy of CBT in sexual offending, including exhibitionism, showed a recidivism rate 40% lower for those taking CBT than for those not receiving treatment (Hanson et al. 2002). Group therapy has also been identified as a successful, cost-effective mode of treatment for exhibitionists. This approach permits patients to discuss their sexual interests and behaviors in a setting that facilitates disclosure and accountability. Being engaged in group therapy is associated with improved prognosis (Morin and Levenson 2008).

Cognitive distortions, such as rationalizing, justifying, and minimizing the sex offense, have been associated with decreased victim empathy (Fedoroff and Marshall 2010; Marshall et al. 2006, W.L. Marshall et al. 2008). By identifying and restructuring these cognitive distortions, the person with exhibitionistic disorder is able to understand the potential impact of the offending behavior on others.

RP strategies for persons with exhibitionistic disorder include the identification of high-risk situations and the pattern of events leading up to offending. They are helped to establish new behaviors and multiple avoidance strategies to interrupt the patterns leading to the offense as early as possible and to avoid high-risk situations. They are also encouraged to develop multiple avoidance strategies in case one strategy is not available or does not work in a situation. For example, an exhibitionist with a pattern of exhibiting from his car on the way home from work might be encouraged to carpool or to speak to his partner by cell phone on the way home. The use of clothing that is not easily removable can also be of assistance (Morin and Levenson 2008).

Pharmacological treatments for exhibitionistic disorder include SSRIs, antiandrogens, and GnRH medications. In most cases, medications are combined with other treatments discussed in this section. A case study of a patient with Huntington's disease and drug-associated exhibitionism noted the successful use of leuprolide in the elimination of deviant sexual fantasies and behaviors (Rich and Ovsiew 1994). SSRIs have also been noted for their successful use in this population (Abouesh and Clayton 1999). However, long-acting GnRH analogues, used in combination with other therapies, have been noted as having the most success in treating exhibitionism, as well as pedophilia and voyeurism (Rösler and Witztum 2000).

Some men arrested for exhibitionism are better understood as public masturbators who are aroused by the idea of getting away with sex in public but who do not intend to be seen. Typically, treatment of public masturbators involves treatment of comorbid psychiatric disorders, including social phobia, alcohol or substance abuse, and inhibited orgasm. It is important to provide social skills training as well as couple's counseling for those who have a sexual partner. Compared with individuals with DSM-5 exhibitionistic disorder, persons who masturbate in public generally respond better to treatment, even without the use of antiandrogens. Of greatest importance is attention to assisting the person to develop law-abiding sexual behaviors that are sexually fulfilling.

Treatment of persons who expose with the hope of proceeding to in-person sexual contact can be further subdivided into those who have been successful with this approach and those who have not. Those who have never been successful and who persist in this activity often have a pervasive developmental delay (e.g., Asperger's disorder) or a significant personality disorder, which

should be the focus of treatment. Of those who expose for sex and have been successful and have come to clinical attention, most are gay men arrested for exposing in public washrooms or parks. Education about the potentially traumatic effect their acts could have on people (especially those who have previously been abused) or about the danger of accidently exposing to children is often sufficient to curtail the behavior, especially if the person is able to find other ways to make contact with sexual partners, such as through the Internet.

Frotteuristic Disorder

Overview

Also referred to as "toucherism," frotteuristic disorder is characterized by sexual urges or fantasies involving sexual touching or rubbing against an unsuspecting person (Box 38–2). Typically, persons with frotteuristic disorder seek out crowded places, such as crowded elevators, subways, or concerts. Approximately 85% of people with frotteurism also have voyeurism or exhibitionism (Aggrawal 2009; Meyer and Weaver 2007). Persons with frotteuristic disorders can be divided into those who are immature and socially unsophisticated and those who are truly preferentially aroused by anonymous contact with an unsuspecting stranger.

Most frotteuristic offenses are not reported to the police (Bradford and Meston 2011). Overcrowding on mass transit and public awareness of the problem in Japan may account for the high reported incidence of frotteuristic offenses in Japan. One survey found that 58.4% of adult women in Japan disclosed having been touched sexually by an unknown person in public (Aggrawal 2009). Regardless of the country in which this occurs, there are three common features of persons with frotteurism: 1) they have large numbers of victims, 2) they are rarely arrested, and 3) when arrested they are rarely given long sentences (Aggrawal 2009).

Box 38–2. DSM-5 Diagnostic Criteria for Frotteuristic Disorder

302.89 (F65.81)

A. Over a period of at least 6 months, recurrent and intense sexual arousal from touching or rubbing against a nonconsenting person, as manifested by fantasies, urges, or behaviors.

B. The individual has acted on these sexual urges with a nonconsenting person, or the sexual urges or fantasies cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

In a controlled environment: This specifier is primarily applicable to individuals living in institutional or other settings where opportunities to touch or rub against a nonconsenting person are restricted.

In full remission: The individual has not acted on the urges with a nonconsenting person, and there has been no distress or impairment in social, occupational, or other areas of functioning, for at least 5 years while in an uncontrolled environment.

Treatment

Few specific case studies have been reported on the treatment of frotteurism. The primary treatment is CBT (Krueger and Kaplan 2008), which focuses on the mediating role of thoughts in creating and maintaining sexual arousal from frotteuristic fantasies and behaviors. Group therapy is often successful because peers can be effective in confronting cognitive distortions while also providing support for nonproblematic behaviors (Krueger and Kaplan 2008).

Krueger and Kaplan (2008) recommend SSRI medications as the primary pharmacological option for treating persons with frotteuristic disorder. A prospective study on the use of MPA in a sample of 275 men incarcerated for sex crimes, including frotteuristic behaviors, also noted that SSRIs had a positive effect on problematic sexual behaviors. Outcome measures included recidivism data (Maletzky et al. 2006). One GnRH agonist (triptorelin) was used successfully in the treatment of frotteuristic disorder occurring together with other paraphilic or criminal behaviors. The triptorelin study was a prospective, uncontrolled, observational study of 30 men with paraphilic disorders treated with triptorelin and psychotherapy. Efficacy of treatment was measured by self-report questionnaires and self-reported sexual fantasies (Rösler and Witztum 1998).

It is important to avoid underestimating how disruptive and distressing frotteurism can be for persons who have this disorder. Like exhibitionism, it is a disorder of urges that can be acted on impulsively and opportunistically. Persons with these disorders often mistakenly think their problem is due to a lack of willpower and are surprised to learn that most people do not need to ward off desires to touch or expose to strangers in public places. They are often responsive to simple education about how traumatic their behaviors can be to their victims. As a general rule, the more sexually driven the frotteuristic behavior is, the more likely it will respond to testosterone-reducing medications. In contrast, if the frotteuristic behavior is motivated by social anxiety or impulsivity, SSRI medications are preferable.

Pedophilic Disorder

Overview

Pedophilic disorder is the most common paraphilia leading to arrest. The DSM-5 diagnostic criteria for pedophilic disorder (Box 38–3) are based on persistent sexual fantasies or desires involving sex with a prepubescent child (typically under age 13). Other characteristics required for diagnosis include being at least age 18 years and at least 5 years older than the victim. Unfortunately, most treatment studies have involved persons with pedophilia who have acted on their interests and been arrested. This has led to confusion regarding persons with pedophilia versus persons who commit a sex crime against a child for reasons that are not sexually motivated. Not all individuals who have sexually abused a child have presentations that meet the DSM-5 criteria for pedophilic disorder. Conversely, not all individuals with a sexual interest in children go on to commit child sexual abuse (Aggrawal 2009; Bradford and Meston 2011; Fedoroff 2008, 2010). The true prevalence of pedophilia is unknown because persons with the disorder are fearful of arrest and often unaware that effective treatment is available.

Box 38–3. DSM-5 Diagnostic Criteria for Pedophilic Disorder

302.2 (F65.4)

A. Over a period of at least 6 months, recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving sexual activity with a prepubescent child or children (generally age 13 years or younger).

B. The individual has acted on these sexual urges, or the sexual urges or fantasies cause marked distress or interpersonal difficulty.

C. The individual is at least age 16 years and at least 5 years older than the child or children in Criterion A.

Note: Do not include an individual in late adolescence involved in an ongoing sexual relationship with a 12- or 13-year-old.

Specify whether:

Exclusive type (attracted only to children)
Nonexclusive type

Specify if:

Sexually attracted to males
Sexually attracted to females
Sexually attracted to both

Specify if:

Limited to incest

Treatment

A survey examining sex offender treatment programs throughout North America indicated that over half of treatment providers use CBT; the second most frequently used approach is RP (Aggrawal 2009). Most research on treatment efficacy for persons with pedophilia uses rates of sexual recidivism as the primary dependent variable. Hanson et al. (2002) conducted a meta-analysis of 43 studies on the effectiveness of psychological treatments of sex offenders as measured by recidivism (both sexual and general). The collective sample included 5,078 treated sex offenders and 4,376 untreated sex offenders. Of the 43 different treatment programs reviewed, 23 were offered in institutions, 17 in the community, and 3 in both settings. The authors were careful to select only studies with good methodological standards. Recidivism was primarily defined as rearrests and/or reconviction. The follow-up periods ranged from 1 to 16 years, with the average being 46 months of opportunity to reoffend. The average rate of sexual recidivism was 12.3% for treated sex offenders, compared with 16.8% for the untreated sample. General recidivism occurred at a rate of 27.9% for treated sex offenders and 39.2% for untreated sex offenders. When only modern programs that included cognitive-behavioral approaches and components of RP were examined, the average sexual recidivism rate for treated sex offenders declined to 9.9%.

L.E. Marshall et al. (2008) reviewed the effectiveness of the sex offender treatment program used in a Canadian federal prison system over the preceding 15 years. The treatment includes components of the Risk/Need/Responsivity (RNR) model and is delivered in a semi-structured cognitive-behavioral and GLM approach that operates on a rolling format so new group members can join at

any time (Marshall et al. 2006). The premise of the RNR model is that success in treatment is most likely when the intensity of the treatment matches the risk of the offender, treatment targets focus on specific criminogenic needs, and treatment is individually modified to match the treatment responses of the patients (Andrews and Bonta 1998). The sample included 534 sex offenders (352 child molesters and 182 rapists) who had been living in the community for an average of 5.42 years. On the basis of the averaged risk levels of the subjects, as measured by the Level of Service Inventory and the Static-99, the expected recidivism rate for the group was 16.8% for sexual recidivism and 40% for general recidivism. Instead, the rates were 3.2% for actual (observed) sexual recidivism rate (1.6% for rapists and 4.0% for child molesters) and 13.6% for general recidivism (Marshall et al. 2006; L.E. Marshall et al. 2008).

Research findings concerning the efficacy of CPA and MPA in treating men with pedophilia are mixed but generally support the use of these medications to reduce sex drive, at least during the initial phases of treatment. Meyer et al. (1992) conducted a study of the effect of MPA and group and individual therapy on adult men. More than half (58%) of the sample were men diagnosed with pedophilia. The subjects were given MPA (400 mg im weekly) for durations ranging from 6 months to 12 years. Results showed that 18% of those receiving MPA reoffended (with the recidivism rates rising to 35% after the medication was discontinued), compared with 55% for the control group. In a double-blind crossover design sample of 19 sexual recidivists with paraphilias, 12 of whom had pedophilia, subjects were either treated with oral CPA or placebo. The dosage of CPA ranged from 50 to 200 mg/day. The use of CPA was associated with a significant reduction in self-report of sexual fantasy and behaviors, physiological responses to deviant stimuli, and levels of circulating sex hormones (Bradford and Pawlak 1993a).

The impact of intramuscular triptorelin and psychotherapy on 30 men with paraphilias, 25 of whom had pedophilia, was examined by Rösler and Witztum (1998). All subjects reported an elimination of all deviant sexual fantasies and desires during triptorelin treatment. Treatment efficacy was measured through self-report questionnaires on intensity of sexual desires and behaviors. The authors concluded that the combined use of long-acting GnRH analogues and psychotherapy is highly effective in the treatment of pedophilia.

Persons with pedophilic disorder limited to incest have an exceptionally favorable prognosis. This is especially true if those incest offenders who target women in order to gain sexual access to their children are excluded from the analysis. As with other paraphilic disorders, the more sexually motivated the behaviors, the more effective treatment with antiandrogens will be.

Conversely, if the offenses always occur when the offender is intoxicated, treatment of the substance abuse may be the most efficacious approach. Sex offenders consistently say they choose victims whom they think will be less likely to report the abuse, so perhaps the most important preventative intervention is to ensure that all children are educated about healthy sexuality and feel comfortable speaking to trusted adults about any sexual concerns.

At the beginning of therapy, many sex offenders with pedophilia are unable to contemplate engaging in a noncoercive sexual and romantic relationship with

anyone. These persons often benefit substantially from antiandrogen treatment that decreases the frequency of intrusive sexual thoughts. However, the aim of treatment for any nonincarcerated man or woman with pedophilia should be to assist them to establish a healthy, prosocial relationship with an appropriate consenting adult partner. Fortunately, the sex drive–suppressing effects of antiandrogens are reversible so it is possible to stop the medication once the former offender and consenting adult partner are ready to resume sexual activity. Many patients with pedophilic disorder are relieved to have their sexual interests suppressed with the voluntary use of antiandrogens and GnRH medications. Persons with pedophilic disorder are rarely exclusively interested in children, and they should be assisted to enhance their sexual interest in adults. Use of legal adult pornography can be of assistance with this aim.

Sexual Sadism Disorder

Overview

Clinically, sexual sadism disorder applies to individuals who derive sexual pleasure from nonconsensual control of another person (Fedoroff 2008). For sexual sadists, the infliction of pain is a means to elicit submission, obedience, fear, and/or humiliation. The key DSM-5 feature of sexual sadism disorder is that the individual experiences clinical distress and interpersonal difficulty from nonconsensual sexual contact with another person (American Psychiatric Association 2013; Bradford and Meston 2011) (Box 38–4). The literature divides sexual sadism into two distinct categories. The first includes people who are interested in the consensual culture of BDSM (bondage-discipline, dominance-submission, and sadomasochism) and who neither cause distress nor are distressed by their interests and activities. The second category includes those who fantasize about and/or commit sexual assaults on nonconsenting victims. The following section on treatment refers only to the second group—sexual sadists aroused by nonconsensual harm to others. Sexual sadism often co-occurs with sexual masochism and sometimes with autoerotic self-asphyxiation, bondage fetishism, and transvestic fetishism (Myers et al. 2008).

Box 38–4. DSM-5 Diagnostic Criteria for Sexual Sadism Disorder

302.84 (F65.52)

A. Over a period of at least 6 months, recurrent and intense sexual arousal from the physical or psychological suffering of another person, as manifested by fantasies, urges, or behaviors.

B. The individual has acted on these sexual urges with a nonconsenting person, or the sexual urges or fantasies cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

In a controlled environment: This specifier is primarily applicable to individuals living in institutional or other settings where opportunities to engage in sadistic sexual behaviors are restricted.

In full remission: The individual has not acted on the urges with a nonconsenting person, and there has been no distress or impairment in social, occupational, or other areas of functioning, for at least 5 years while in an uncontrolled environment.

Treatment

Criminal sexual sadism is by definition dangerous to others. Therefore, treatment begins by ensuring that current and potential victims are safe from harm. Sadists who are aroused by fantasies or acts involving nonconsensual behaviors require definitive treatment to ensure they do not act on their interests. If the fantasies are sexually motivated, antiandrogens are very helpful. It is important for clinicians to distinguish between true sexual sadists and patients who present with sadistic fantasies or behaviors that are secondary to major mental illnesses such as mood disorders or schizophrenia. Persons with sexual sadism enjoy their fantasies. In contrast, persons who present with sadistic thoughts that are secondary to mental illness typically are upset by their sadistic fantasies. For example, persons with mood disorders may adopt the identity of a sex offender because it is compatible with a depression-induced change in self-attitude. Their assumed self-image involves being, for example, the "worst person in the world." These patients respond best to treatment with antidepressant medications and CBT directed at their mood disorder. CBT for sexual offenders, including those with criminal sexual sadism, typically uses the RNR model of rehabilitation.

The role of testosterone and androgens in aggression is well established (Bradford 2000). Antiandrogens, CPA, and MPA have been effective in reducing sexual fantasies and behaviors in persons with paraphilic disorders, including sexual sadism (Bradford 2000; Bradford and Pawlak 1993a, 1993b; Rösler and Witztum 2000). A German study by Briken et al. (2000) examined the use of luteinizing hormone–releasing hormone in the treatment of sexual aggression in a group of 11 participants with sexual sadism and pedophilia. Results indicated a reduction in sexually aggressive behavior and a reduction in deviant sexual arousal, as measured by phallometry. Case reports have also noted the utility of SSRIs to successfully decrease sexual aggression and deviant sexual interests (Bradford 2000; Rösler and Witztum 2000).

It is important for clinicians not to confuse sexual sadists who have nonconsensual interests with persons who identify themselves as interested in "safe, sane, and consensual" sex (BDSM practitioners). Research on a community-based sample found that almost 2% of the sample had been involved in some form for BDSM activity in the previous year (Richters et al. 2008). Persons in the BDSM category typically do not require treatment because their sexual interests are based on consent. However, some individuals or couples with BDSM interests seek counseling because of either concerns about being stigmatized or unfounded worries about possible deterioration into criminal behavior. Education to correct this misconception is often all that is needed. Another reason to recommend couples therapy is when only one partner is interested in BDSM activities and the other is not.

Sadistic behaviors that are sexually motivated respond well to antiandrogen medications. If compliance is a concern and the patient is voluntary, GnRH medications are indicated. During the first month of initiating GnRH medications, many experts also prescribe an antiandrogen to prevent a possible increase in testosterone at the beginning of GnRH therapy. Individual, group, and/or couples therapy is important to monitor progress and to enhance prosocial sexual behaviors.

Voyeuristic Disorder

Overview

It is important for clinicians to distinguish between true voyeurism and normal arousal from observing nudity or sexual activity. In interviews with noncriminal heterosexual men, 54.3% reported sexual fantasies of secretly witnessing others having sexual intercourse; 40.4% also reported a sexual interest in themselves being secretly observed during intercourse. In most instances these men's descriptions would not meet the clinical criteria for voyeuristic disorder (Aggrawal 2009). Voyeuristic disorder is characterized by sexual urges or fantasies of observing unsuspecting and nonconsenting persons who may be in various stages of undress or sexual activity (Box 38–5). Persons with voyeuristic disorder are aroused from the time they leave their apartment at night in search of a window with a light on. In contrast, persons without voyeurism might become aroused by accidentally seeing a naked person in a window, but their arousal is due to the nudity rather than to the nonconsensual nature of the situation. In some cases persons with voyeurism are also aroused by fear of being caught while they are engaging in voyeuristic acts (Aggrawal 2009). True voyeurs typically are not sexually aroused by attending a strip bar or a "peep show" because the dancers know they are being watched and there is no threat of being detected or arrested.

Box 38–5. DSM-5 Diagnostic Criteria for Voyeuristic Disorder

302.82 (F65.3)

A. Over a period of at least 6 months, recurrent and intense sexual arousal from observing an unsuspecting person who is naked, in the process of disrobing, or engaging in sexual activity, as manifested by fantasies, urges, or behaviors.
B. The individual has acted on these sexual urges with a nonconsenting person, or the sexual urges or fantasies cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The individual experiencing the arousal and/or acting on the urges is at least 18 years of age.

Specify if:

In a controlled environment: This specifier is primarily applicable to individuals living in institutional or other settings where opportunities to engage in voyeuristic behavior are restricted.

In full remission: The individual has not acted on the urges with a nonconsenting person, and there has been no distress or impairment in social, occupational, or other areas of functioning, for at least 5 years while in an uncontrolled environment.

Treatment

The majority of the published literature on the treatment of voyeurism is based on case studies. Some treatment success for persons with voyeurism has been noted from treatment using RP combined with CBT. Treatment targets include cognitive restructuring of offense-specific thoughts, interpersonal and social skills training, coping skills, improving self-confidence, and developing victim empathy to undermine the arousal associated with voyeuristic activities. Success has also been noted with therapeutic approaches that focus on controlling impul-

sivity, improving social relationships, and identifying and facilitating healthier modes of sexual gratification (Aggrawal 2009).

Bradford (2000) recommends that in cases in which there is no in-person contact between offender and victim, such as in cases of voyeurism, pharmacological treatments should begin with combined use of CBT and RP with SSRIs. He suggests that other pharmacological approaches, including antiandrogens, should be used only after these measures have proven unsuccessful. A case study by Abouesh and Clayton (1999) examined the effect of paroxetine in a patient with voyeurism. Before treatment the patient reported sexual thoughts and anxiety prior to acting on his urges. Feelings of relief were noted immediately after acting on the fantasy. The patient took paroxetine 10 mg at bedtime for 4 weeks. He described improvement in his ability to control his voyeuristic acts but still reported recurring thoughts of voyeurism. After the dose of paroxetine was raised to 20 mg, he reported a noticeable decline in the intensity of his voyeuristic urges and fantasies. Other research on the pharmacological treatment of voyeurism identifies the combined use of long-acting GnRH analogues and RP as highly effective (Rösler and Witztum 2000).

Persons with voyeuristic disorder rarely seek treatment until they have been caught. It is important for clinicians to establish that the aim of treatment is to assist in modifying the sexual interest into one in which there is consent. Education about the difference between normal arousal from seeing a naked person and arousal from spying on a nonconsenting victim can be helpful. Patients with voyeuristic disorder should always be asked about other paraphilic interests, especially frotteurism and exhibitionism. It is very important to establish whether the patient has considered entering another person's house or has done so, because this can be indicative of a nonconsensual sadistic sexual interest. Education about the harm their acts can cause to others is helpful. SSRIs, antiandrogens, and GnRH medications can assist until the person is able to establish a consensual relationship, at which time the medication can be cautiously tapered. The mainstay of treatment is assisting the person to establish prosocial relations that are sexually fulfilling.

Paraphilias and Paraphilic Disorders Not Involving Criminal Activities or Situations

Fetishistic Disorder

Overview

Sexual fetishistic disorder involves a persistent sexual interest in nonsexual inanimate objects or specific body parts (Box 38–6). Typically, the fetishistic object is used in masturbation or incorporated into sexual play. Sexual stimulation can come from smelling, tasting, or fondling the object of desire. Because the object is often strongly preferred or required for sexual arousal, sexual dysfunctions may occur if inclusion of the fetish does not occur. Fetishism is not generally associated with criminality but may lead to occupational, interpersonal, or social impairment (Bradford and Meston 2011). Fetishistic objects often include but are not limited to women's undergarments, shoes, feet, and leather.

Box 38–6. DSM-5 Diagnostic Criteria for Fetishistic Disorder

302.81 (F65.0)

A. Over a period of at least 6 months, recurrent and intense sexual arousal from either the use of nonliving objects or a highly specific focus on nongenital body part(s), as manifested by fantasies, urges, or behaviors.

B. The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The fetish objects are not limited to articles of clothing used in cross-dressing (as in transvestic disorder) or devices specifically designed for the purpose of tactile genital stimulation (e.g., vibrator).

Specify:

Body part(s)
Nonliving object(s)
Other

Specify if:

In a controlled environment: This specifier is primarily applicable to individuals living in institutional or other settings where opportunities to engage in fetishistic behaviors are restricted.

In full remission: There has been no distress or impairment in social, occupational, or other areas of functioning for at least 5 years while in an uncontrolled environment.

The prevalence of fetishism is unknown because most fetishes do not require treatment or come to the attention of law enforcement officials, unless the individual commits a crime, such as breaking and entering, to obtain the fetishistic item(s). However, the large number of Internet forums, chat rooms, and pornography sites suggest that subclinical fetishism is not rare (Bradford and Meston 2011). The most common paraphilias co-occurring with fetishism include pedophilia and transvestic fetishism (Aggrawal 2009).

Treatment

Prior to the start of treatment of fetishistic disorder, the clinician needs to clarify the patient's goals for treatment: reduction of all deviant sexual interests, reduced reliance on the fetishistic object, elimination of criminal activity associated with the fetish, and/or increased sexual interest in intimate relationships (Darcangelo et al. 2008). The most frequent behavioral treatment is aversive conditioning, which associates the fetishistic object or fantasy with nausea-inducing drugs and mild electric shock. One case study emphasized the use of an aversive unconditioned stimulus and reinforcing stimuli to successfully counter-condition a fetish (Darcangelo et al. 2008). In a study of 70 males and 6 females with fetishism that used a combined approach of directive guidance, behavioral modification, and rational-emotive therapy over a 14-session period, 91% of the sample responded favorably to the treatment and reported a reduction in the harmful effects associated with the fetish (Lowenstein 1998).

Behavioral reconditioning must always be offered in the context of informed and revocable consent, with specific treatment goals. It is both inef-

fective and unethical if administered as punishment.

When the patient has a romantic partner, couples therapy can be very helpful, especially if partner dissatisfaction is a motivation for treatment. A primary treatment goal is to decrease the interference imposed by the fetish on the couple's sexual relationship. Rooted within sex therapy, the use of sensate focus exercises and communication training has been found to be successful (Darcangelo et al. 2008). When there is less reliance on the fetishistic object, the couple tends to report increased satisfaction with the relationship. By ensuring that certain levels of sexual excitement are maintained, reliance on the fetishistic object tends to be limited (Darcangelo et al. 2008). However, it is important to be aware that a change in fetishistic interest or reliance on the fetishistic object can result in a significant change in the sexual relationship, which may not be welcomed by the person's sexual partner(s).

Many persons with fetishes are ashamed of their sexual interests. Many enter into sexual relationships hoping they can cure themselves, and many probably do. Although fetishistic disorders are by definition persistent, they do not deteriorate, and it is often helpful to educate patients about the benign nature of most fetishes. In fact, the most harmful aspect of most fetishes involves the secrecy and deception they can bring to relationships. It is often helpful to educate the patient's partner, who may worry that if he or she did not know about the patient's shoe fetish, the patient might be keeping other secrets. Treatment is most effective when it focuses on improving the relationship. Sometimes, patients persist in their wish to explore pharmacological treatments; it is important to be sure the patient is making this decision freely and voluntarily. Further comments about the treatment of fetishes can be found in the subsection "Transvestic Disorder" later in this section.

Sexual Masochism Disorder

Overview

Sexual masochism disorder is characterized by sexual arousal from the fantasy or experience of involuntarily being psychologically or physically beaten, bound, humiliated, or made to suffer (Box 38–7). An interest in sexual masochism typically includes submission in response to embarrassment, or control through bondage, regulations, or commands. Pursued activities may include spanking, whipping, and paddling (Aggrawal 2009). As discussed in the subsection "Sexual Sadism Disorder" earlier in this chapter, it is important for clinicians to distinguish between persons who have masochistic interests that they engage in via "safe, sane, and consensual" activities (known as BDSM) and persons with masochistic disorder whose interests involve activities that diminish the ability of either sexual partner to consent. Examples of persons with masochism who may benefit from clinical treatment include those who engineer sexual scenarios in which they may be killed, those who force their partners to engage in sadistic acts against their will, and those whose masochistic interests are so extreme that they are unable to establish consensual sexual relationships. DSM-5 includes asphyxiophilia as a subtype of sexual masochism even though sexual arousal from restriction of breathing can be independent of masochism.

Box 38–7. DSM-5 Diagnostic Criteria for Sexual Masochism Disorder

302.83 (F65.51)

A. Over a period of at least 6 months, recurrent and intense sexual arousal from the act of being humiliated, beaten, bound, or otherwise made to suffer, as manifested by fantasies, urges, or behaviors.

B. The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

With asphyxiophilia: If the individual engages in the practice of achieving sexual arousal related to restriction of breathing.

Specify if:

In a controlled environment: This specifier is primarily applicable to individuals living in institutional or other settings where opportunities to engage in masochistic sexual behaviors are restricted.

In full remission: There has been no distress or impairment in social, occupational, or other areas of functioning for at least 5 years while in an uncontrolled environment.

Sexual masochism often co-occurs with other paraphilias, including fetishism, transvestic fetishism, and sexual sadism. Sexual masochism disorder is by definition persistent. Some individuals, especially those coming to clinical attention, increase the severity of masochistic acts over time or during periods of increased stress (Aggrawal 2009).

Treatment

Some persons with sexual masochism disorder present for treatment with concerns that their paraphilic sexual interests are interfering with their everyday activities or social or sexual relations. Others have clinical concerns related to feelings of shame, guilt, and self-loathing. Such feelings can be associated with depression (Fedoroff 2010).

Historically, some treatment success has been noted with behavioral therapies, including aversion therapy, orgasmic reconditioning, and covert sensitization (reviewed in Fedoroff 2008, 2010). However, contemporary approaches use more cognitive-behavioral techniques and interpersonal therapies to target depression and social withdrawal (Fedoroff 2008, 2010). One case study of the treatment of a sexual masochist reviewed a number of treatments, including psychotherapy, aversion therapy, SSRIs, and antiandrogens. In this case, the use of antiandrogens seemed to provide improvement, although short term. The authors noted the need to treat the patient's social isolation (Shiwach and Prosser 1998).

It is important for clinicians to identify suicidal interests and behaviors in patients presenting with a chief complaint of masochism. Typically, concerns about masochistic interests arise in the context of problems in relationships (e.g., a concerned husband worried about his wife's masochistic requests). Many patients present with unwelcome masochistic fantasies, often involving fantasies of death, as a result of mood disorders. Some become unwilling participants in masochistic activities at the insistence of a sadistic partner. It is important to diagnose and treat any underlying psychiatric disorders and to pay attention to relationship problems. The key to therapy in clinically significant masochism is to help the patient become aware of the fact

that sadism and masochism, rather than being at opposite ends of a continuum, are more like a continuous circle in which extreme masochism and extreme sadism are virtually indistinguishable. Treatment is aimed at helping patients take control of their sexual behaviors by enhancing aspects of their sexual selves that improve rather than diminish their sexual fulfillment. Pharmacological interventions for extreme masochism disorders are the same as those discussed earlier in this chapter for sadistic sexual disorders.

Transvestic Disorder

Overview

DSM-5 presents three varieties of transvestism: transvestic disorder (distressing sexual arousal from wearing clothes of the opposite sex), transvestic disorder with fetishism (involving arousal from fabrics, materials, or garments), and transvestic disorder with autogynephilia (involving arousal from thinking or imagining oneself as female) (Box 38–8). Typically, but not always, persons with transvestic disorder are heterosexual men who become sexually aroused while wearing women's clothing and undergarments. In most instances, the interest in lingerie begins in childhood and becomes sexualized during puberty. Transvestism is significantly more prevalent in biological males than females (Aggrawal 2009). This paraphilia can co-occur with gender identity disorder, masochistic disorder, and autoerotic self-asphyxia (hypoxyphilia) (Fedoroff 2010).

Box 38–8. DSM-5 Diagnostic Criteria for Transvestic Disorder

302.3 (F65.1)

A. Over a period of at least 6 months, recurrent and intense sexual arousal from cross-dressing, as manifested by fantasies, urges, or behaviors.
B. The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

With fetishism: If sexually aroused by fabrics, materials, or garments.
With autogynephilia: If sexually aroused by thoughts or images of self as female.

Specify if:

In a controlled environment: This specifier is primarily applicable to individuals living in institutional or other settings where opportunities to cross-dress are restricted.
In full remission: There has been no distress or impairment in social, occupational, or other areas of functioning for at least 5 years while in an uncontrolled environment.

Treatment

Some individuals with transvestic disorder present for treatment with distress related to being "found out," others are struggling with how to explain their sexual interests to a new partner, and still others present with a desire to rid themselves of this interest altogether. For those wishing to decrease or eliminate their interest in transvestism, combined use of RP, harm reduction, and GLM has been suggested (Marshall et al. 2006). The harm reduction approach functions on the understanding that ending all incidents of cross-dressing may be difficult, but works to reduce the frequency and severity of such behavior when it does

occur. GLM emphasizes adaptive functioning and balanced lifestyle. The goal is to identify a positive sexual goal, such as enhancing adult sexual relationships, and increase the frequency and salience of that interest and behavior rather than only using avoidance techniques (e.g., avoiding lingerie shops).

According to Hayes et al. (2003), for individuals who present with distress regarding their transvestism, acceptance and commitment therapy (ACT) is an appropriate treatment. The ACT approach can be used to clarify personal values and to work toward patients' acceptance of their distress while they strive to live a life consistent with their personal values. Within the ACT approach, cross-dressing may alleviate stress or provide solace in an otherwise uneventful day. It fosters the ability to live with the distress without becoming consumed by it.

If the person voluntarily wishes to eliminate dependence on cross-dressing, low-dose SSRI medications are often effective. In contrast, cross-dressing due to gender identity issues is typically not responsive to pharmacotherapy (Fedoroff and Marshall 2010; Marshall et al. 2006). The most frequent medications noted among case reports of cross-dressing are SSRIs and anxiolytics (Fedoroff 2010). In some cases, treating concurrent mood and anxiety problems alleviates concerns related to transvestism. For example, in a case study, a 24-year-old man with bipolar disorder and transvestism was treated with lithium, and the transvestism symptoms were eliminated (Ward 1975). Fedoroff (1988) reported a case study (described above in the section on SSRIs) in which a 46-year-old man with transvestism and general anxiety disorder was successfully treated with buspirone. Of note in that case was the fact that the patient's wife noticed he was less "tuned out" when they engaged in sexual relations, which the patient explained was because he no longer had to fantasize about being cross-dressed in order to stay sexually aroused with his wife. His transvestic interests returned when he stopped the medication and remitted again when he resumed the medication in an ABA design.

The clinician always needs to establish the reasons the patient wishes to cross-dress. Men with gender identity disorder often wear female clothing to present themselves publicly in their female gender role. Others may dress as women to attract men to whom they are sexually interested. Men with transvestism by definition wear female clothing to accentuate sexual arousal. Typically, they lose all interest in wearing the female clothing as soon as they reach orgasm. In contrast, transsexuals wear female clothing while engaging in nonsexual activities. Some men start off as transvestites, wearing women's clothing only when they are masturbating, but as they age their interest in wearing women's clothing at other times becomes more prominent. It is important to educate patients and their partners about the fact that cross-dressing says nothing about their sexual orientation or about their ability to parent. The clinician should always ask patients with transvestism if they engage in autoerotic asphyxiation because the two conditions often co-occur and can lead to accidental death.

Patients with transvestic disorder who wish to try pharmacological treatment should be given a trial of SSRI. It is important to use a dosage that is high enough to be effective but low enough not to cause inhibited orgasm, because then patients often resort to their previous paraphilic fantasies and behaviors to facilitate orgasm. Often, patients and their spouses are reassured when they

learn that the paraphilia is both prevalent and nonprogressive. Responsivity to pharmacological treatment suggests that transvestism may have a physiological etiology, and this observation is often comforting to patients and their spouses. In the case of the man who responded to buspirone (Fedoroff 1988), who was mentioned earlier in this section, on follow-up it was discovered that he had stopped taking the medication and had experienced a return of his transvestic interests. He explained that he kept a bottle of the pills in his cupboard but, because he and his wife knew the pills were there, neither of them felt a need for him to take the medication. He said that his wife had agreed to incorporate lingerie into their sex life and both felt this was the best outcome.

Other Specified Paraphilic Disorder and Unspecified Paraphilic Disorder

Overview

The diagnosis of other specified paraphilic disorder (OSPD) is intended to cover the more than 100 other paraphilic disorders that have been described (Fedoroff 2010). DSM-5 specifically lists sexual arousal involving telephone scatologia (obscene phone calls), necrophilia (corpses), zoophilia (animals), corprophilia (feces), klismaphilia (enemas), and urophilia (urine) (Box 38–9). Unspecified paraphilic disorder is intended to refer to all other situations in which the criteria for specified disorders are inadequate (Box 38–10).

Box 38–9. DSM-5 Other Specified Paraphilic Disorder

302.89 (F65.89)

This category applies to presentations in which symptoms characteristic of a paraphilic disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the paraphilic disorders diagnostic class. The other specified paraphilic disorder category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for any specific paraphilic disorder. This is done by recording "other specified paraphilic disorder" followed by the specific reason (e.g., "zoophilia").

Examples of presentations that can be specified using the "other specified" designation include, but are not limited to, recurrent and intense sexual arousal involving *telephone scatologia* (obscene phone calls), *necrophilia* (corpses), *zoophilia* (animals), *coprophilia* (feces), *klismaphilia* (enemas), or *urophilia* (urine) that has been present for at least 6 months and causes marked distress or impairment in social, occupational, or other important areas of functioning. Other specified paraphilic disorder can be specified as in remission and/or as occurring in a controlled environment.

Box 38–10. DSM-5 Unspecified Paraphilic Disorder

302.9 (F65.9)

This category applies to presentations in which symptoms characteristic of a paraphilic disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the paraphilic disorders diagnostic class. The unspecified paraphilic disorder category is used in situations in which the clinician chooses *not* to specify the reason that

the criteria are not met for a specific paraphilic disorder, and includes presentations in which there is insufficient information to make a more specific diagnosis.

Treatment

Most individuals with OSPD never present for treatment. The main reason is that in most cases OSPD and unspecified paraphilic disorder do not cause sufficient problems to warrant concern. Other reasons include shame, lack of knowledge that treatment is available, and the mistaken assumption that treatment will not work. Some individuals mistakenly worry that if they disclose their unconventional sexual interests, they will be labeled as potential sex offenders.

A case study of a male with a history of telephone scatologia and exhibitionism notes the successful use of covert sensitization and CBT. The study was a prospective multiple-baseline design that examined physiological responses through penile tumescence testing, self-report, and collateral information. The treatment eliminated all interest in scatologia and significantly reduced incidents of exhibitionism (Alford et al. 1980). The use of psychoeducation regarding risks of ingesting various substances led to improvement in cases of oral partialism and urophilia (McGuire et al. 1998). McNally and Lukach (1991) discussed the successful treatment of a man with mild mental retardation who masturbated in front of a dog. Treatment in this case study included masturbatory satiation, covert sensitization, and contingency management procedures. Treatment outcome was measured through patient self-report.

Conclusion

Individuals who present with concerns about unconventional sexual interests should be reassured that there is a wide range of sexual interests and that most are not harmful. They should be informed about the duty of clinicians to report known sexual abuse of vulnerable children and other vulnerable people (e.g., individuals with intellectual disability). This caution often helps the patient to feel safe about disclosing his or her own sexual concerns. Once the disclosure has been made, it is very important to tell the patient that his or her particular interest is well known (as it almost always is) (Fedoroff 2010). Often, there is a Web site in which the condition is described. The person should be questioned concerning other paraphilic interests, especially those involving potentially criminal interests or self-harm. It is always helpful to explore why the person decided it was time to seek help.

Paraphilic disorders, by definition, are due to persistent anomalous sexual interests; however, paraphilic behaviors are voluntary and do not become more persistent when the behavior is stopped. Modern treatments that focus on establishing new and healthier sexual interests have an excellent success rate.

This chapter includes a cursory overview of the treatment options available for a variety of paraphilias. Space limitations prevent a more complete discussion and require that references be kept to a minimum. We hope that the main themes of this chapter are clear:

- Paraphilias are widespread and are often the cause of clinical concern.
- Most people with paraphilic disorders are not criminals, and vice versa.
- Treatment is available.
- More than one type of treatment is available, and treatment methods are synergistic.
- Treatment of paraphilic disorders usually works.

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CHAPTER 39

Gender Dysphoria

Anne A. Lawrence, M.D., Ph.D.

Persons who experience persistent, clinically significant distress about their anatomic sex or assigned gender role have been recognized since antiquity. In DSM-5 (American Psychiatric Association 2013), these individuals can be diagnosed with *gender dysphoria.* The DSM-5 diagnostic criteria for gender dysphoria in adults appear in Box 39–1. Persons with presentations that meet diagnostic criteria for gender dysphoria in DSM-5 would have received a different DSM diagnosis—usually either *transsexualism* or *gender identity disorder* (GID)—prior to 2013. Consequently, some expert recommendations and empirical studies relevant to the treatment of adults with gender dysphoria refer instead to persons with transsexualism or GID. A brief explanation of these terms is therefore indicated.

Box 39–1. DSM-5 Diagnostic Criteria for Gender Dysphoria in Adolescents and Adults

302.85 (F64.1)

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:

1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).

6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).

Coding note: Code the disorder of sex development as well as gender dysphoria.

Specify if:

Posttransition: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen—namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

When disorders involving distress about anatomic sex or assigned gender role first entered DSM in 1980 (DSM-III; American Psychiatric Association 1980), they appeared under the superordinate category *gender identity disorders.* Their defining feature was said to be "an incongruence between anatomic sex and gender identity" (p. 261), where *gender identity* referred to a person's fundamental sense of being male or female. Adults with persistent discomfort about their anatomic sex and a desire to live as members of the opposite sex could receive a diagnosis of *transsexualism* in DSM-III and DSM-III-R (American Psychiatric Association 1987). They can still receive this diagnosis in the *International Statistical Classification of Diseases and Related Health Problems,* 10th Revision (ICD-10; World Health Organization 1992). Males and females with transsexualism are often referred to as *male-to-female* (MtF) and *female-to-male* (FtM) transsexuals. In DSM-IV and DSM-IV-TR (American Psychiatric Association 1994, 2000), the diagnosis of transsexualism was replaced by the diagnosis of *gender identity disorder*; as a result, this term applied to both the superordinate category and a specific diagnosis within that category.

It has long been recognized that not all adults with GID (the superordinate category) have presentations that meet full diagnostic criteria for transsexualism or GID (the specific diagnosis). Accordingly, both ICD and DSM have consistently provided one or more residual diagnoses for persons with nonclassical or *nontranssexual* types of GID. These diagnoses could be applied to individuals whose presentations fulfilled some but not all diagnostic criteria for transsexualism or GID (i.e., who were *subthreshold* for these diagnoses) or who had alternative gender identities but did not identify as the opposite sex (e.g., men who identified as *eunuchs* and sought only castration, not complete sex reassignment; Johnson et al. 2007). In the DSM-5 diagnostic criteria for gender dysphoria, the new term *experienced/expressed gender*—a neologism for *gender identity*—encompasses a wider range of identities than just the opposite sex. Consequently, it appears that many persons who would previously have been diagnosed with residual or nontranssexual forms of GID would now be diagnosed with gender dysphoria. DSM-5 nevertheless includes two residual diagnoses for persons whose presentations do not meet full criteria for gender

dysphoria: *other specified gender dysphoria* and *unspecified gender dysphoria.* The DSM-5 descriptions of these diagnoses appear in Boxes 39–2 and 39–3.

Box 39–2. DSM-5 Other Specified Gender Dysphoria

302.6 (F64.8)

This category applies to presentations in which symptoms characteristic of gender dysphoria that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for gender dysphoria. The other specified gender dysphoria category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for gender dysphoria. This is done by recording "other specified gender dysphoria" followed by the specific reason (e.g., "brief gender dysphoria").

An example of a presentation that can be specified using the "other specified" designation is the following:

The current disturbance meets symptom criteria for gender dysphoria, but the duration is less than 6 months.

Box 39–3. DSM-5 Unspecified Gender Dysphoria

302.6 (F64.9)

This category applies to presentations in which symptoms characteristic of gender dysphoria that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for gender dysphoria. The unspecified gender dysphoria category is used in situations in which the clinician chooses *not* to specify the reason that the criteria are not met for gender dysphoria, and includes presentations in which there is insufficient information to make a more specific diagnosis.

Because the diagnosis of gender dysphoria is so broadly encompassing, it is useful to distinguish between adults with gender dysphoria who experience *transsexualism* and those who experience *nontranssexual* forms of gender dysphoria. These terms are relatively unambiguous and remain widely used both in clinical settings and in the scientific literature (e.g., Hembree et al. 2009), even though transsexualism has not been a formal DSM diagnosis since 1994. The term *transgender* can be used to denote persons with significant cross-gender identification or gender-atypical feelings or behaviors, whether or not they meet diagnostic criteria for gender dysphoria.

Gender Dysphoria in Adults

Guidelines for the treatment of adults with gender dysphoria were originally developed for the treatment of transsexualism. Clinicians recognized in the 1970s that most persons with transsexualism could not be successfully treated using conventional psychotherapeutic techniques (Gijs and Brewaeys 2007). They could often be significantly helped, how-

ever, by sex reassignment: hormonal, surgical, and social/legal interventions that would allow them to physically resemble and live as members of the opposite sex. The first expert consensus guidelines for the treatment of persons seeking sex reassignment were the Standards of Care (SOC) for the treatment of persons with gender dysphoria, first published in 1979 (Walker et al. 1990). The SOC emphasized a multidisciplinary approach to the treatment of transsexualism, involving the coordinated participation of mental health professionals, hormone-prescribing physicians, and surgeons. This approach has remained a central feature of subsequent revisions of the SOC (e.g., Meyer et al. 2001; World Professional Association for Transgender Health [WPATH] 2011), as well as guidelines developed by the Endocrine Society (Hembree et al. 2009) and independent experts (e.g., Gooren 2011). The stated goal of treatment for persons with gender dysphoria under the SOC was "lasting personal comfort with the gendered self in order to maximize overall psychological well-being and self-fulfillment" (Meyer et al. 2001, p. 3).

The SOC and similar guidelines for the multidisciplinary treatment of transsexualism and gender dysphoria have typically emphasized five principal therapeutic elements:

1. Assessment of gender dysphoria and any coexisting mental health issues
2. Psychotherapy
3. Real-life experience (RLE) in the desired gender role
4. Cross-sex hormone therapy
5. Sex reassignment surgery (SRS) to make the primary and secondary sex characteristics of the body resemble those of the desired sex

In MtF transsexuals, SRS usually refers to feminizing genitoplasty. In FtM transsexuals, SRS can refer to either breast reduction with chest reconstruction or masculinizing genitoplasty.

Although multidisciplinary, multielement therapy for persons with gender dysphoria was originally developed to treat transsexualism, the same approach was subsequently extended to nontranssexual forms of gender dysphoria, with the understanding that many nontranssexuals would not need or want all elements of therapy. It was recognized, for example, that some nontranssexual persons with gender dysphoria sought cross-sex hormone therapy but did not want SRS (Gijs and Brewaeys 2007). All editions of the SOC have consistently stated that hormone therapy, RLE, and nongenital forms of SRS, separately or in combination, can be appropriate treatment for both transsexual and nontranssexual forms of gender dysphoria, but that genital SRS should be reserved for patients who have successfully completed a 1-year, full-time RLE and (usually) 1 year of cross-sex hormone therapy.

Most experienced practitioners follow the SOC, but the recommendations therein are based almost entirely on expert consensus, not a higher quality of evidence (Byne et al. 2012). Moreover, a few studies have suggested that patients whose treatment deviated significantly from the SOC reported outcomes as good as or better than those whose treatment complied fully with the SOC (Lawrence 2003; Pimenoff and Pfäfflin 2011).

Natural History of Gender Dysphoria in Adults: Treatment Implications

A common belief, including among some experts, is that transsexualism in adulthood "is generally an unalterable condition" (Gooren 2011, p. 1251). In reality,

the natural history of severe gender dysphoria in adults is incompletely understood, but its outcomes appear to be both variable and not easily predictable. Carroll (1999) observed that some adults diagnosed with gender dysphoria eventually come to accept their natal sex and gender role; this process may involve integration of their cross-gender feelings into unique, nontraditional gender identities (WPATH 2011). Other persons with gender dysphoria find that part-time cross-gender expression offers a satisfactory solution (e.g., living in cross-gender role only at home or while on vacation). Still other persons—perhaps up to one-half of adults who begin evaluation or psychotherapy for gender dysphoria—withdraw from treatment, with the result that their outcomes are unknown (Carroll 1999). Consequently, patients and treating professionals should not assume that complete gender transition with hormonal and surgical sex reassignment is the inevitable outcome for adults diagnosed with transsexualism or severe gender dysphoria.

Role of Mental Health Professionals

Mental health professionals play an essential role in the multidisciplinary treatment of gender dysphoria and transsexualism in adults. They not only conduct the necessary assessments and provide psychotherapy but also supervise and document the patient's RLE and serve as referral sources and gatekeepers for the provision of hormone therapy and surgical care by providing letters of recommendation to hormone-prescribing physicians and to surgeons.

In consequence, mental health professionals are often called on to play a more complex and multifaceted role in the treatment of adults with gender dysphoria than is typical in the treatment of patients with other psychiatric disorders. Several articles and reports (e.g., Bockting 2008; WPATH 2011) offer detailed analyses of tasks that mental health professionals are sometimes expected to perform in the course of treatment, such as the following:

- Assessing the dimensions and severity of gender dysphoria
- Assessing, diagnosing, and treating comorbid psychiatric conditions
- Providing psychotherapy addressing gender dysphoria and related issues
- Educating patients regarding treatment options, including possible medical and surgical treatments
- Ascertaining patients' readiness for medical and surgical treatments
- Initiating referrals for medical and surgical treatments
- Consulting and collaborating with treating medical and surgical professionals
- Educating family members and partners about gender dysphoria and facilitating psychotherapy for them as needed

Assessment of Gender Dysphoria and Comorbid Mental Health Issues in Adults

Careful psychological assessment is the initial step in the treatment of adults with gender dysphoria. Patients with gender dysphoria often consult mental health professionals to confirm their self-diagnoses, clarify their gender identities, formulate goals, or obtain referrals for hormone therapy or SRS. Sometimes patients may be referred for assessment after first contacting a hormone-prescribing physician or surgeon. Making the diagnosis

of gender dysphoria, assessing its dimensions and severity, determining the patient's ability to understand and consent to various treatment options, and diagnosing and treating any comorbid psychiatric problems are among the most important goals of this process. Comorbid psychiatric disorders do not necessarily preclude treatment of gender dysphoria, but adequate assessment of gender dysphoria may not be possible if certain disorders (e.g., schizophrenia or major depressive disorder) are not adequately managed. Treatment of comorbid conditions may also be required if patients are to give meaningful informed consent to hormonal and surgical treatment.

An important part of the evaluation of adults with gender dysphoria is the determination of the subtype of gender dysphoria with reference to sexual orientation; such a determination facilitates case conceptualization and informs prognosis. Subtypes based on sexual orientation unfortunately were not included in the diagnostic criteria for gender dysphoria in DSM-5 but were part of the criteria for transsexualism and GID in the four previous versions of DSM (Lawrence 2010); their omission from DSM-5 does not diminish their importance. The sexual orientation of persons with gender dysphoria may be either *homosexual* relative to natal sex (exclusively oriented toward persons of the same biologic sex) or *nonhomosexual* relative to natal sex (oriented toward persons of the opposite sex, both sexes, or neither sex). Compared with their nonhomosexual counterparts, homosexual MtF transsexuals report more cross-gender behavior during childhood and less transvestic fetishism or sexual arousal to the thought or image of being female (*autogynephilia;* Blanchard 1991). Homosexual MtF transsexuals also seek treatment at younger ages, and their appearance is more congruent with their gender identity (Lawrence 2010). Several studies have suggested that homosexual MtF and FtM transsexuals display better psychological functioning after sex reassignment and also report more favorable subjective outcomes (Lawrence 2010).

Psychotherapy for Adults With Gender Dysphoria

The role of psychotherapy in the treatment of gender dysphoria in adults has evolved over time. During the first half of the twentieth century, clinicians understood transsexualism to be a psychological problem for which psychological treatment was the only appropriate therapy (Gijs and Brewaeys 2007). The failure of psychoanalytic psychotherapy to cure or improve most patients with transsexualism eventually led to acceptance of the radical but effective techniques of hormonal and surgical sex reassignment. In the 1979 edition of the SOC (Walker et al. 1990), psychotherapy was relegated to a minor role in the treatment of transsexualism; its primary purpose was to establish patients' eligibility for the hormonal and surgical interventions that were believed to constitute the effective elements of treatment. In later editions of the SOC (e.g., Meyer et al. 2001; WPATH 2011), psychotherapy received increased emphasis and assumed a larger role. Byne et al. (2012) proposed that the low rates of regret following SRS in recent years might be partly attributable to psychotherapy. Lawrence (2003) observed, however, that MtF transsexuals who rated their preoperative psychotherapy as "adequate" did not report better subjective outcomes after SRS than those who did not; moreover, informants who reported more hours of preoperative psychotherapy experienced less improvement in quality of life after SRS.

The most effective techniques and methods of psychotherapy for adults with gender dysphoria are matters of disagreement. There is a general consensus that psychotherapy cannot be expected to eliminate or cure gender dysphoria (WPATH 2011). It is recognized, however, that some persons with gender dysphoria who undergo psychotherapy become more comfortable with their natal sex or gender role, decide not to pursue sex reassignment (Meyer et al. 2001, p. 8), or at any rate discontinue treatment (Carroll 1999; Smith et al. 2005). Persons with gender dysphoria who decide to live in cross-gender role usually must deal with stigma and discrimination and often experience significant losses (e.g., the breakup of important relationships or termination of employment). It is generally agreed that psychotherapy during the RLE can help persons who are good candidates for sex reassignment deal with these inevitable challenges by providing support, promoting resilience, and assisting in the development of interpersonal skills and coping strategies (Byne et al. 2012; WPATH 2011). Seikowski (2007) concluded that intensive psychotherapy (e.g., psychoanalysis, depth psychotherapy, behavioral therapy) was not necessary for most patients with gender dysphoria but was indicated for those with serious psychopathology, who represented about one-third of the patients he studied.

Morris (2007) offered a pessimistic summary of the difficulties inherent in offering intensive psychodynamic psychotherapy to patients with severe gender dysphoria or transsexualism. He observed that most such patients do not expect to benefit from psychotherapy and will not accept the idea that their desire for sex reassignment might be, at least in part, symptomatic of unconscious intrapsychic conflict. Also, the attitudes that inform contemporary treatment paradigms are not easily reconciled with those underlying psychodynamic therapy: a patient's belief that he or she genuinely is or can become a member of the opposite sex could be considered delusional from a psychodynamic perspective, but it is not considered delusional "among gender disorder–friendly mental health workers, where arguably the belief is a cultural norm" (Morris 2007, p. 94). Morris concluded that although patients with gender dysphoria or transsexualism need and deserve the help that psychodynamic psychotherapy can provide, few patients are likely to be willing or able to take advantage of it.

Experienced therapists operating from other theoretical perspectives have been more optimistic and have described a variety of approaches to psychotherapy for adults with gender dysphoria or transsexualism. Pfäfflin (2007) emphasized the value of attentive listening, awareness of countertransference reactions, and willingness to "acknowledge and accept *any* form of presentation of gender-identity related distress" (p. 177). He argued that mental health professionals have an obligation not to confront patients with doubts about their ability to pass in their desired gender role; if patients themselves express such doubts, however, he believed it was usually productive to address them. Fraser (2009) described an approach combining object-relations and self-psychology paradigms and discussed the importance of empathetically mirroring the patient's transgender feelings—which typically were hidden and therefore inaccessible to mirroring earlier in life—within the supportive "holding environment" of the therapeutic relationship. Bockting (2008) recommended that therapists devote particular attention to addressing the negative effects of stigma and transphobia. He also suggested that therapists should actively encourage their

patients to abandon the unrealistic goal of "changing sex" and instead embrace their own unique transgender identities:

> The desire to change sex fully is common; however, in reality, changing sex in such a binary way is neither attainable nor fulfilling.… Psychotherapy can aid in grieving the loss of the ideal to make room for a deeper level of acceptance of one's transgender (as opposed to male or female) identity. The task of the mental-health professional is to recognize the client's despair while simultaneously beginning to challenge "passing" as the overriding goal. (p. 216)

Note that Bockting's (2008) belief that it is sometimes the therapist's obligation to challenge the patient's goals (e.g., the goal of successfully passing as the opposite sex) stands in contrast to Pfäfflin's (2007) recommendation that the therapist adopt a nonconfrontational approach.

Under the multidisciplinary treatment model described earlier (see introductory text in the section "Gender Dysphoria in Adults" earlier in this chapter), case management can be conceptualized as an element of psychotherapy. Patients who want to begin hormone therapy or undergo SRS usually rely on their psychotherapists to evaluate their eligibility and readiness and to initiate referrals to qualified practitioners. Smith et al. (2005) found that psychotherapists were more likely to recommend hormone therapy for patients with more severe gender dysphoria, better psychological stability, and a physical appearance more congruent with the desired sex. Psychotherapists also routinely provide psychoeducation to their patients with gender dysphoria. Therapists are well positioned to explain various treatment options and to help patients consider the pros and cons of each, assuming that they themselves are familiar with the techniques, risks, and benefits of hormone therapy and SRS. As noted earlier, providing education about gender dysphoria to spouses, partners, and family members and initiating referrals for counseling or psychotherapy where indicated are also tasks ordinarily performed by psychotherapists.

Real-Life Experience in the Desired Gender Role

The term *real-life experience* (RLE) was used in the 1998 and 2001 editions of the SOC to denote "the act of fully adopting a new or evolving gender role or presentation in everyday life" (Meyer et al. 2001, p. 25). The term does not appear, however, in the 2011 edition of the SOC, which simply discusses the option of "living in a gender role that is congruent with one's gender identity" (WPATH 2011, p. 58). Nevertheless, the term is still widely used in clinical practice and the published literature. Some patients with gender dysphoria or transsexualism will already be living full-time in a cross-gender role (or in their desired gender role) when first seen by clinicians.

The RLE was originally called the *real-life test*, because it allowed patients to test their belief that living in the gender role of the opposite sex would offer them a better quality of life. A 1-year RLE has always been an eligibility requirement for genital SRS under the SOC, but the essential ingredients of an RLE that would confer such eligibility have never been set forth in detail. In the 1998 and 2001 versions of the SOC, acquiring "a (legal) gender-identity-appropriate first name" (Meyer et al. 2001, p. 25) was one unambiguous requirement, but this became optional in the 2011 edition. Living in a gender role congruent with one's gender identity—the language employed in the 2011 SOC—would seem to be almost entirely open to individual interpretation.

The RLE was used as an eligibility requirement for genital SRS based on the belief that it was a "fully reversible" step that, if successful, would give patients and their caregivers confidence about undertaking subsequent irreversible steps (Meyer et al. 2001). However, whereas the RLE itself may be reversible, its social and economic consequences—loss of employment, for example—may not be reversible, even if the person returns to living in the original gender role. Most males with gender dysphoria who undergo sex reassignment will never be able to pass inconspicuously as women in all social situations (Levine 2009). Perhaps as a result, some men with gender dysphoria find ways to undergo SRS after an abbreviated RLE (Lawrence 2003) or without any RLE.

The RLE is often credited with reducing the prevalence of regrets after SRS; "however, in reality, little empirical evidence supporting this claim exists" (Bockting 2008, p. 218). Levine (2009) likewise noted "the absence of a firm scientific foundation to support the utility and validity of the RLE" (p. 186). The RLE is, of course, not unique in this respect: many recommended elements of treatment for gender dysphoria or transsexualism are based primarily on expert consensus rather than on rigorous empirical evidence (Byne et al. 2012).

Cross-Sex Hormone Therapy for Adults With Gender Dysphoria

Cross-sex hormone therapy promotes the development of the secondary sex characteristics of the opposite sex and partially suppresses the secondary sex characteristics of a person's natal sex (Hembree et al. 2009). Feminizing hormone therapy for MtF transsexuals and other males with gender dysphoria typically consists of an estrogen (administered orally, transdermally, or intramuscularly), often accompanied by an antiandrogen such as oral spironolactone or cyproterone acetate (Gooren 2011; Hembree et al. 2009). Alternatively, parenteral gonadotropin-releasing hormone (GnRH) analogues can be used in combination with estrogen, but they are usually prohibitively expensive. Feminizing hormone therapy usually results in breast development, reduction in body hair, suppression of male-pattern scalp hair loss, decreased muscle mass, increased subcutaneous fat deposition, decreased sexual interest and arousability, and reduced fertility (Hembree et al. 2009). Facial hair is largely unaffected by feminizing hormones, and MtF transsexuals usually undergo facial depilation with electrolysis, laser, or pulsed-light treatments. Feminizing hormone therapy is often experienced as emotionally calming, and hormone-treated MtF transsexuals display improved psychological adjustment in comparison to untreated individuals (Leavitt et al. 1980).

Masculinizing hormone therapy for FtM transsexuals and other females with gender dysphoria typically consists of only intramuscular or transdermal testosterone. Masculinizing hormone therapy usually causes growth of facial hair and male-typical body hair, deepening of the voice, male-pattern scalp hair loss, enlargement of the clitoris, increased muscle mass, increased sexual interest and arousability, decreased fertility, and suppression or elimination of menses. Masculinizing hormone therapy also has emotional and psychological effects, including an increased tendency to aggressiveness and anger (van Goozen et al. 1995).

Gender attribution depends primarily on the presence or absence of male-typical physical traits; female-typical physical traits are much less relevant

(Kessler and McKenna 1978). Persons who display visible signs of physical masculinization are usually regarded as male. To be regarded as female, individuals must display few or no visible signs of physical masculinization. Because testosterone is very effective at inducing masculinization, hormone-treated FtM transsexuals usually have little problem being perceived as male. In contrast, because estrogen is relatively ineffective at reducing the signs of masculinization that men develop during puberty, hormone-treated MtF transsexuals often have great difficulty being perceived as female.

These difficulties notwithstanding, a review of 28 published studies involving 1,093 hormone-treated MtF transsexuals and 801 hormone-treated FtM transsexuals (Murad et al. 2010) concluded that hormone therapy—accompanied by other treatment modalities in many cases—is associated with significant improvement in gender dysphoria, psychological symptoms and comorbid conditions, quality of life, and sexual function in both MtF and FtM transsexuals. In a study whose results were consistent with these conclusions, Gorin-Lazard et al. (2012) observed that MtF and FtM transsexuals who were treated with cross-sex hormones but who had not yet undergone SRS reported significantly better quality of life than their counterparts who had not received hormone therapy. Hormone therapy can be associated with significant medical complications, especially in MtF transsexuals. Wierckx et al. (2012) reported that among 50 hormone-treated MtF patients, 3 (6%) experienced thromboembolic events and another 3 (6%) experienced other cardiovascular complications, including 2 myocardial infarctions; one-quarter of the MtF patients also had evidence of osteoporosis. In contrast, the 50 hormone-treated FtM transsexuals in the Wierckx et al. study did not experience significant cardiovascular events or other complications.

Sex Reassignment Surgery

Techniques of genital SRS for MtF transsexuals have been perfected over many decades and routinely produce excellent cosmetic and functional results (Gijs and Brewaeys 2007). The most common technique involves orchiectomy, penectomy, creation of a neovagina lined with penile and scrotal skin, vulvoplasty using genital skin, and creation of a sensate clitoris from part of the glans penis. In carefully selected candidates, MtF SRS is associated with high levels of patient satisfaction and minimal regrets (Gijs and Brewaeys 2007; Lawrence 2003). In the only prospective controlled investigation of MtF SRS outcomes, Mate-Kole et al. (1990) found that patients who received SRS on an expedited schedule reported better psychosocial outcomes than wait-listed control patients. Good surgical results and absence of complications are among the factors most strongly associated with subjective satisfaction and lack of regret after MtF SRS (Lawrence 2003).

MtF transsexuals often undergo nongenital surgery in connection with sex reassignment. Facial feminization surgery typically involves reduction of the size or prominence of the brow ridge, nose, mandible, and laryngeal cartilage. These male-typical features are minimally affected by cross-sex hormone therapy, and surgical treatment often greatly improves the patient's ability to be perceived as female. MtF transsexuals often request breast augmentation if estrogen-induced breast development has been inadequate.

Breast reduction with chest reconstruction is the first, the most important, and sometimes the only SRS procedure that FtM transsexuals undergo (Monstrey et

al. 2007). It is commonly performed before the patient begins the RLE, because passing as male is otherwise often very difficult. The goal of surgery is not merely the removal of unwanted breast tissue, but "the creation of an aesthetically pleasing male chest" (Monstrey et al. 2007, p. 137). With careful choice of surgical technique, most patients experience satisfactory and often very good results.

Genital SRS for FtM transsexuals is more problematic. Because there are no really satisfactory surgical techniques, many FtM transsexuals decide to forgo genital SRS entirely. Two techniques are currently the most popular. In *radial forearm flap phalloplasty*, a skin graft from the forearm is used to create a tube-within-a-tube neophallus that is attached at the perineum via microsurgery. This technique results in a phallus of normal size that has protective and erogenous sensation and that usually permits standing urination (Monstrey et al. 2007). Unfortunately, radial forearm flap phalloplasty has a moderately high rate of complications, even in expert hands; it is also prohibitively expensive for most patients if the procedure is not covered by insurance. In *metoidioplasty*, the hypertrophied clitoris is used to create a microphallus; standing urination is sometimes possible if the urethra is surgically lengthened (Monstrey et al. 2007). The compromises inherent in metoidioplasty—primarily the small size and limited function of the resulting phallus—are offset by the technique's simplicity, relative freedom from complications, and comparative affordability. With either of these techniques, a neoscrotum can be constructed from labial skin, and testicular prostheses can be inserted.

Results of Sex Reassignment

Most studies of the results of sex reassignment generally and SRS specifically have concluded that these treatments are associated with significant relief of gender dysphoria, a high degree of patient satisfaction, few instances of regret, and generally favorable psychosocial outcomes (Gijs and Brewaeys 2007; Lawrence 2003; Murad et al. 2010; Smith et al. 2005). Nevertheless, one long-term follow-up study found higher mortality from suicide and increased risks of suicide attempts and psychiatric hospitalizations for MtF and FtM transsexuals relative to non-gender-dysphoric controls (Dhejne et al. 2011). These results suggest that MtF and FtM transsexuals remain at increased risk for psychiatric problems after sex reassignment, notwithstanding the relief of gender dysphoria they usually experience. Smith et al. (2005) concluded that sex reassignment is an effective treatment for gender dysphoria and that its outcomes are generally favorable, but that FtM transsexuals and those whose sexual orientations were homosexual relative to natal sex achieved better results. Risk factors for less satisfactory postoperative functioning in both MtF and FtM patients included nonhomosexual orientation, greater comorbid psychopathology, and greater body dissatisfaction (Smith et al. 2005).

Gender Dysphoria in Children

Natural History of Gender Dysphoria in Children: Treatment Implications

The diagnostic criteria for gender dysphoria in children are provided in Box 39–4.

Box 39–4. DSM-5 Diagnostic Criteria for Gender Dysphoria in Children

302.6 (F64.2)

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):
   1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
   2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
   3. A strong preference for cross-gender roles in make-believe play or fantasy play.
   4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
   5. A strong preference for playmates of the other gender.
   6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
   7. A strong dislike of one's sexual anatomy.
   8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).

Coding note: Code the disorder of sex development as well as gender dysphoria.

The appropriate treatment for children with gender dysphoria is a topic characterized by uncertainty and controversy. There is little reliable information—and certainly none in the form of randomized controlled trials—concerning the outcomes of any treatment options, much less a range of possible treatment options. Indeed, there is surprisingly little consensus among parents and caregivers even concerning the desired outcomes of treatment. There is, however, a considerable body of evidence concerning the natural history of gender dysphoria in children, with potential implications for treatment.

It is generally agreed that most children with untreated gender dysphoria will not continue to experience significant gender dysphoria or request sex reassignment when they reach adulthood. Instead, their gender dysphoria will usually remit or disappear, a phenomenon called *desistence.* Only a minority of children with gender dysphoria will experience *persistence* of gender dysphoria into adulthood. Green's (1987) long-term follow-up study of feminine boys, most of whom probably would have met diagnostic criteria for gender dysphoria, was among the first to demonstrate this:

of 44 boys seen at follow-up in late adolescence or adulthood, 75%–80% had a homosexual or bisexual orientation, but only 1 displayed persistent gender dysphoria. In a follow-up study of 25 girls with childhood GID, of whom 60% had presentations that met full diagnostic criteria and 40% had presentations that were subthreshold, Drummond et al. (2008) reported that only 3 (12%) experienced persistent gender dysphoria in late adolescence or adulthood; 8 (32%) were classified as homosexual or bisexual on the basis of sexual attraction. In another follow-up study, Wallien and Cohen-Kettenis (2008) observed somewhat higher persistence rates: of 59 boys with gender dysphoria, 12 (20%) were still gender dysphoric in late adolescence or adulthood, whereas of 18 girls with gender dysphoria, 9 (50%) were still gender dysphoric. Nearly all those with persistent gender dysphoria displayed a homosexual or bisexual orientation in adulthood, as did all of the females and half of the males whose gender dysphoria desisted. Wallien and Cohen-Kettenis observed that persistence was more likely in children with more severe gender dysphoria. In short, whereas a homosexual or bisexual orientation is a frequent outcome of gender dysphoria in childhood, persistent gender dysphoria is an infrequent outcome.

The fact that gender dysphoria in children usually desists by adolescence is, of course, an insufficient basis for suggesting that treatment is unnecessary: many medical and psychiatric conditions characterized by painful but time-limited symptoms are routinely treated, sometimes very intensively, because their symptoms are so distressing while present. Nevertheless, the self-limited nature of most cases of gender dysphoria in children suggests that the relative risks and benefits of treatment need to be weighed carefully.

Disagreements About Objectives of Treatment for Children With Gender Dysphoria

The overall goal of treatment for children with gender dysphoria is to promote the child's well-being and psychological adjustment (Byne et al. 2012). Beyond this, there is little consensus about specific objectives of treatment, other than attempting to identify and address any comorbid psychopathology. Comorbid psychiatric conditions are not unusual in children with gender dysphoria. In a study of 120 Dutch children with a complete or subthreshold diagnosis of GID, Wallien et al. (2007) reported that 62 (52%) had one or more other DSM psychiatric diagnoses—about the same as in a comparison group of children with attention-deficit hyperactivity disorder (ADHD). About 31% of the children with GID had comorbid anxiety disorders, 6% had mood disorders, and 23% had disruptive disorders (ADHD or conduct disorder).

Arguably the most fundamental area of disagreement in the treatment of gender dysphoria in children concerns whether or not attempting to promote the desistence of gender dysphoria and thereby prevent transsexualism in adulthood is an appropriate treatment goal. Both Byne et al. (2012) and Zucker (2008) observed that the opinions that experienced clinicians hold on this and closely related issues typically reflect their beliefs concerning the etiology, significance, and potential malleability or immutability of gender identity in children with gender dysphoria. Some clinicians, whom Zucker called "biological essentialists" (p. 359)—but who would probably describe themselves as "gender affirming"—believe that the transgender identities of children with gender dysphoria are fundamentally

biological, although they concede that environmental factors may also play some role. For example, Ehrensaft (2012) argued that "the kernel of gender identity…is there from birth, residing within us in a complex of chromosomes, gonads, hormones, hormone receptors, genitalia, but most importantly in our brain and mind" (p. 341). Consistent with this point of view, Ehrensaft's treatment approach involved empowering gender-variant children to express, insofar as possible, their "true gender selves," which reflected the gender identities that she believed to be resident in their brains and minds. Zucker (2008), in contrast, argued that biological factors do not determine gender identity but merely constitute predisposing temperamental influences. He believed that other factors also contribute to the development of gender dysphoria in children, including psychopathology in the child, psychopathology in the parents, disturbed attachment relations between child and parents, and parental reinforcement or tolerance of the child's cross-gender behavior (see also Meyer-Bahlburg 2002). Because many of these factors are potentially modifiable using techniques that are not ethically problematic, Zucker contended that encouraging desistence of the child's gender dysphoria and thereby attempting to prevent transsexualism in adulthood were feasible and appropriate goals of treatment.

Areas of Consensus in the Treatment of Gender Dysphoria in Children

Given the disagreements among experts about goals and methods of therapy and the limited evidence available, Byne et al. (2012) concluded that it was possible to offer no more than "general suggestions and cautions" (p. 772) regarding the appropriate treatment of gender dysphoria in children. Many of these suggestions concerned the importance of informing parents and caregivers (and, as appropriate, children themselves) about the limitations of current knowledge and the lack of consensus among experts. Parents should be informed about the range of treatment goals and therapeutic options available, the disagreements and uncertainties surrounding these, and the absence of reliable empirical evidence concerning the efficacy and outcomes of treatment. They should also be told about the range of possible developmental trajectories in children with gender dysphoria, with or without treatment: persistence, partial desistence, or complete desistence of gender dysphoria; the elevated probability of a homosexual or bisexual orientation in adulthood; and the small but non-negligible possibility of a desire for sex reassignment in adulthood. Byne et al. further proposed that clinicians should be mindful that parents may pressure them for a "normalizing" solution, which might involve demands for either premature gender transition or elimination of all gender-atypical behaviors.

In the absence of expert consensus on specific therapeutic methods, it may be useful to first consider the approaches used in the gender clinics in Amsterdam and Toronto, which have the most extensive experience in treating children and adolescents with gender dysphoria (Byne et al. 2012), and then compare some alternative approaches.

Amsterdam Approach to Gender Dysphoria in Children

As described by de Vries and Cohen-Kettenis (2012), the Amsterdam approach

to the treatment of children with gender dysphoria emphasizes "watchful waiting and carefully observing how gender dysphoria develops in the first stages of puberty" (p. 301). The process begins with interviews involving the child and parents, together and separately. The goal is not only to establish a formal diagnosis but also to understand the intensity and expression of the child's gender dysphoria. There is also assessment of the child's intellectual and psychological functioning, including the presence of any comorbid psychopathology or symptoms that may be consequences of gender dysphoria (e.g., depression or social anxiety).

In the Amsterdam approach, treatment is not directed toward the child's gender dysphoria per se but rather toward any psychological problems in the child or the family that appear to influence or contribute to gender dysphoria (e.g., conflicts with parents or siblings). De Vries and Cohen-Kettenis (2012) proposed that psychotherapy and counseling for the child can encourage development of positive self-esteem and assist the child in dealing with the critical reactions of others to cross-gender expression, even if therapy does not lead to a resolution of gender dysphoria. They also emphasized the importance of parent counseling. Overall, their advice to parents tends to be fairly conservative regarding the child's cross-gender expression, given the observation that most cases of gender dysphoria in children will desist. For example, de Vries and Cohen-Kettenis recommend that children not make a full social transition to the other gender (i.e., not fully change name, personal pronouns, or clothing) prior to early puberty, largely to avoid the problems involved in returning to the original gender role if the child's gender dysphoria desists. Regarding this recommendation, they cited observations by Steensma et al. (2011) concerning the difficulties experienced by some children whose social presentations had been typical of the opposite sex and in whom GID had desisted: "Some girls, who were almost (but not even entirely) living as boys in their childhood years, experienced great trouble when they wanted to return to the female gender role" (Steensma et al. 2011, p. 514). De Vries and Cohen-Kettenis also advise parents to encourage their child with gender dysphoria to have ongoing contact with children and adults of the child's natal sex and to participate in gender-typical social activities. They do not suggest that parents completely prohibit gender-variant behavior, but rather that they impose sensible limits that will protect the child from bullying and harassment.

Toronto Approach to Gender Dysphoria in Children

Zucker et al. (2012b) explained that the treatment model used at the Gender Identity Service at the Centre for Addiction and Mental Health in Toronto views cross-gender identity in children as a biopsychosocial phenomenon with a variety of possible developmental trajectories. Initial assessment involves interviews with the parents and child, together and separately. Clinicians also administer or employ 19 different psychological tests, assessment tasks, and questionnaires in the usual assessment protocol. Case conceptualization is premised on the theory that, whereas the gender identities of most children may be fixed and unchangeable, the cross-gender or gender-variant identities of children with gender dysphoria are potentially more malleable. This is particularly true when children's gender-variant identities are caused or sustained by specific psychosocial influences, such

as parental reinforcement of gender-variant behavior, disturbed social cognition (i.e., concerning what it means to be a boy or a girl), comorbid psychopathology (e.g., separation anxiety or obsessional tendencies associated with autism spectrum disorders), or the operation of unconscious psychological mechanisms in response to past traumatic experiences or unresolved conflict within the family.

Treatment typically involves a combination of weekly play psychotherapy for the child, weekly counseling or psychotherapy for the parents, parental interventions in the home environment, and treatment of comorbid psychiatric problems with medication when indicated (Zucker et al. 2012b). Play psychotherapy allows children with gender dysphoria the opportunity to express and "make sense of their internal representational world" (Zucker et al. 2012b, p. 383) in a supportive, minimally structured environment. Psychotherapy with parents focuses on parental factors that may play a role in the origin and continuation of cross-gender behavior (e.g., identification with the opposite-sex parent as a response to parent-child conflict or a parent's emotional withdrawal). Parental interventions in the home involve both setting limits on cross-gender behaviors and facilitating improved relations with same-sex peers; the latter can involve parental organization of play dates with same-sex children who are temperamentally compatible with the child or enrollment of the child in community activities (e.g., sports or gymnastics) in the case of older children.

Other Treatment Approaches to Gender Dysphoria in Children

Meyer-Bahlburg (2002) described a treatment protocol for boys with gender dysphoria that had some elements in common with the Amsterdam and Toronto approaches but differed in certain important respects. For example, to avoid stigmatizing the child, only the parents were seen in formal therapy sessions. Treatment was conducted by the parents in the home environment and involved strengthening the father-son relationship, giving positive attention to gender-typical or gender-neutral behaviors and neither positive nor negative attention to gender-atypical behaviors, improving relationships with same-sex peers through parent-organized play dates with temperamentally compatible boys, and enlisting the cooperation of persons outside the immediate family to decrease opportunities for cross-gender behavior outside the home (e.g., cross-dressing at the home of an aunt or grandmother or at nursery school). Meyer-Bahlburg (2002) reported that in 10 out of 11 consecutive cases, there was marked improvement—namely, apparent resolution of symptoms—after a median of 10 parent treatment sessions.

Ehrensaft (2012), whose opinions about the biological roots of gender identity were discussed earlier (see subsection "Disagreements About Objectives of Treatment for Children With Gender Dysphoria" in this section), characterized her therapeutic approach as reflecting an "oppositional" (p. 338) rather than an alternative clinical model. Among other things, she rejected the idea that the symptoms of gender dysphoria are pathological, arguing, for example, that a boy who "dreams of being a girl when he grows up is not a child with a disorder, but rather a child who is creatively weaving his own gender web" (p. 339). Although Ehrensaft acknowledged the possibility that childhood gender nonconformity can sometimes result from trauma or disturbed attachment relationships, she stated that this was uncommon

in her experience. Her approach involves encouraging the child to explore and express his or her "authentic gender identity" (p. 339) while developing the psychological capacity to deal with situations in which that authentic gender identity cannot safely be expressed. Much of the therapeutic work involves helping the child's parents deal with their feelings and learn how to better support their transgender child. In contrast to the Amsterdam and Toronto models, Ehrensaft's therapeutic model allows for and sometimes encourages full-time social transition to the preferred gender role prior to adolescence.

Although they did not describe a comprehensive approach to the treatment of children with gender dysphoria, Edwards-Leeper and Spack (2012) argued that at least some children with gender dysphoria should be allowed to transition socially prior to adolescence. Like Ehrensaft (2012), they seemed to conceptualize GID as a biologically based phenomenon, approvingly noting "the increasingly common belief that a transgender individual's…brain (or soul) has always been his or her affirmed gender" (p. 322). Edwards-Leeper and Spack stated that, in the case of children with a strong desire to transition to the opposite gender role, "our clinical recommendation is that every effort be made to support the child by allowing them [sic] to live in their affirmed gender to the extent that it is deemed safe" (p. 330). While acknowledging the concerns expressed by Steensma et al. (2011) about possible difficulties in returning to the gender role associated with the child's natal gender after an early transition, Edwards-Leeper and Spack were reassured by the observation that "we have not seen any detrimental effects of early social transitioning in our patient population when done in a thoughtful way" (p. 331).

Gender Dysphoria in Adolescents

Natural History of Gender Dysphoria in Adolescents: Treatment Implications

The diagnostic criteria for gender dysphoria in adolescents are identical to those applicable to adults (see Box 39–1). Although gender dysphoria usually desists without treatment in children, the probability of desistence in adolescents with gender dysphoria is much lower. Many cases of gender dysphoria in adolescence represent the continuation of gender dysphoria that began in childhood; notably, when childhood gender dysphoria desists, this usually occurs between ages 10 and 13 years (Steensma et al. 2011). Consequently, it is reasonable to expect that gender dysphoria that begins in childhood and persists past early adolescence will continue to persist into adulthood unless effectively treated. Some adolescents with gender dysphoria, however, do not have a history of gender dysphoria in childhood. Zucker et al. (2011) observed,

> In clinics such as ours, we see some adolescents with GID who show little or absolutely no evidence of GID in early childhood. In many respects, these adolescents resemble the "late-onset" form of GID that has been described in the literature on adults (see Lawrence 2010). The gender dysphoria appears to emerge, at least in the eyes of significant others (e.g., parents, therapists who have known the patient since childhood) only after the onset of puberty. (p. 63)

Zucker et al. noted that it was not clear whether adolescents with gender dysphoria without a history of gender dysphoria in childhood should be eligible

for early (puberty-suppressing) hormone therapy, a treatment that is described later in this chapter (see subsection "Puberty-Suppressing Hormones for Adolescents With Gender Dysphoria"). Edwards-Leeper and Spack (2012) likewise called attention to this subset of "atypical" adolescents with gender dysphoria having a comparatively recent onset of symptoms but did not discuss whether their treatment should differ.

Overview of Treatment of Gender Dysphoria in Adolescents

Many of the treatment elements applicable to adults with gender dysphoria are also applicable to adolescents with gender dysphoria. These include assessment (confirming the diagnosis of gender dysphoria, characterizing its features, and evaluating comorbid psychopathology), psychotherapy, RLE in the desired gender role, and hormone therapy. Hormone therapy for adolescents with gender dysphoria involves the use of puberty-suppressing hormones, not cross-sex hormones. Adolescents with gender dysphoria typically become eligible for cross-sex hormone therapy at age 18, or at age 16 in some European countries. Byne et al. (2012) observed that the gender clinics in Amsterdam and Toronto, both of which see large numbers of adolescents with gender dysphoria and have systematically collected and published relevant data, can serve as important sources of information and expertise concerning appropriate treatment.

Assessment of Gender Dysphoria and Comorbid Conditions in Adolescents

Both the Amsterdam and Toronto clinics emphasize the importance of assessing not only the adolescent's gender dysphoria but also any coexisting psychiatric problems. Comorbid psychopathology is common in adolescents with gender dysphoria: de Vries et al. (2011a) found that among 105 Dutch adolescents with gender dysphoria, 32% had one or more comorbid DSM diagnoses, including 22% with anxiety disorders, 13% with mood disorders, and 12% with disruptive disorders (ADHD and oppositional defiant disorder). Zucker et al. (2012a) observed that adolescents with GID displayed more severe behavioral problems than comparison groups of clinically referred and nonreferred adolescents. Both the Amsterdam and the Toronto clinics believe that adolescents with significant comorbid psychological problems should be treated for these other conditions and followed over time to see whether this treatment will reduce their desire to undergo sex reassignment (Byne et al. 2012). In the most recent SOC, WPATH (2011) suggests that psychoeducation should also be an element of assessment, because "the way that adolescents respond to information about the reality of sex reassignment can be diagnostically informative" (p. 15), especially in the case of adolescents who have unrealistic expectations.

Over the last decade, adolescents referred to the Toronto clinic for gender dysphoria, especially males, have become more diverse with respect to sexual orientation (Zucker et al. 2012a). Consequently, determination of subtype based on sexual orientation (homosexual vs. nonhomosexual, relative to natal sex) may be an important element of assessment and case conceptualization for adolescents with gender dysphoria, especially for males. These subtypes were applicable to postpubertal or sexually mature adolescents with transsexualism or GID in the last four versions of DSM.

In Toronto, Zucker et al. (2012a) observed that 45% of 105 adolescent males with gender dysphoria, versus only 24% of 87 adolescent females with gender dysphoria, were classified as nonhomosexual on the basis of fantasy. Among other characteristics, nonhomosexual males with gender dysphoria displayed fewer behavioral problems, were less severely gender dysphoric, displayed less cross-gender behavior, and reported more sexual arousal with cross-dressing than their homosexual counterparts. Nonhomosexual females with gender dysphoria likewise were less severely gender dysphoric and displayed less cross-gender behavior than their homosexual counterparts. Subtypes based on sexual orientation were significantly associated with recommendations for puberty-suppressing hormones in the Toronto program: 73% of homosexual applicants with gender dysphoria received a positive recommendation, versus only 44% of nonhomosexual applicants (Zucker et al. 2011). Comparable data are not available from Amsterdam, because adolescents with persistent gender dysphoria who have been treated there have been, almost without exception, exclusively homosexual (Wallien and Cohen-Kettenis 2008; Steensma et al. 2011).

Psychotherapy and Real-Life Experience for Adolescents With Gender Dysphoria

Both the Amsterdam and Toronto clinics offer supportive psychotherapy and psychoeducation to their adolescent patients with gender dysphoria. As is the case with adults, the intent of psychotherapy with adolescents is not to cure the gender dysphoria but rather to encourage patients to explore their options and ensure that they are adequately informed about possible outcomes (Byne et al. 2012). Many adolescents with gender dysphoria, especially those with long-standing symptoms, will already be living full-time in their preferred gender role when they are seen for evaluation and psychotherapy. Other adolescents, especially males with a late-onset (and possibly nonhomosexual) type of gender dysphoria, "do not appear to have considered how they would begin to present themselves as the other gender and often create a sense of dissonance in the examiners between their wish and their appearance" (Byne et al. 2012, p. 775).

Assessment and psychotherapy result in a recommendation for puberty-suppressing hormones for some adolescents with gender dysphoria, but not for all. The Amsterdam clinic supports full-time transition to the preferred gender role and a recommendation for puberty-suppressing hormones for adolescents with long-standing gender dysphoria who have good parental support and no significant psychopathology (de Vries and Cohen-Kettenis 2012). Smith et al. (2001) reported outcomes in 20 adolescents with gender dysphoria who were approved for hormone treatment and eventual SRS under the Amsterdam protocol and 21 adolescents who were not. The principal reason for a decision not to recommend treatment was an inability to arrive at a diagnosis of transsexualism; usually this was not because the adolescents in question were found to be subthreshold for the diagnosis, but rather because "in many of these cases the psychological or environmental problems were too serious to make an accurate diagnosis" (p. 473). In the Smith et al. study, 65% of the adolescents in the treated group were females, whereas 62% of the adolescents in the untreated group were males. When

assessed at follow-up an average of 3–4 years later, both groups reported less gender dysphoria; Smith et al. interpreted these results as implying that their decisions about who should be offered treatment and who should not had been sensible ones.

According to Byne et al. (2012), the Toronto clinic tends to support full-time transition and puberty-suppressing hormones for adolescents with long-standing gender dysphoria but maintains a stance of "neutrality" (p. 773) concerning transition for adolescents with a recent onset of gender dysphoria or significant comorbid psychopathology. Zucker et al. (2011) reported that, based on logistic regression analysis, Toronto clinicians were more likely to recommend puberty-suppressing hormones for adolescents who displayed fewer behavioral problems, more intense gender dysphoria, and more extreme cross-gender behavior, currently and during childhood. Clinicians were also more likely to recommend hormones for females and, as noted previously, for adolescents with a homosexual orientation, but these variables were not significant predictors in the logistic regression analysis, probably because they were so closely associated with more extreme cross-gender behavior, which was a stronger predictor.

Puberty-Suppressing Hormones for Adolescents With Gender Dysphoria

The use of puberty-suppressing hormones for adolescents with severe gender dysphoria or transsexualism was pioneered in the Netherlands. In the early 1990s, some adolescents evaluated in the Amsterdam clinic who had severe, long-standing gender dysphoria that seemed unlikely to desist were observed to be extremely distressed by the physical changes of puberty and were struggling with social and psychological problems that seemed to be caused by their gender dysphoria rather than being merely comorbid with it (Kreukels and Cohen-Kettenis 2011). In response to their situation, the clinic adopted an investigational treatment protocol that made these adolescents eligible for cross-sex hormones at age 16, rather than age 18, as had been the policy previously. The results of treatment using this protocol were encouraging: the patients experienced relief of gender dysphoria, functioned well psychologically, and did not regret early treatment. Moreover, clinicians observed that patients who had begun treatment before reaching the final stage of puberty achieved an appearance more congruent with their preferred gender than did patients who had begun hormone treatment in adulthood (Kreukels and Cohen-Kettenis 2011).

Based on this experience, the Amsterdam clinic developed a second treatment protocol for adolescents with severe gender dysphoria, in which parenteral GnRH analogues were used to suppress or block the physical changes of puberty. GnRH analogues prevent the release of pituitary gonadotropins that stimulate the production of testosterone or estradiol (Kreukels and Cohen-Kettenis 2011; see also Gooren 2011; Hembree et al. 2009). The effects of GnRH analogues are fully reversible; pubertal development will resume spontaneously and rapidly if they are discontinued (Hembree et al. 2009). However, not one of more than 100 adolescents who have been treated with GnRH analogues in the Amsterdam program has ever chosen to discontinue treatment (de Vries and Cohen-Kettenis 2012; Kreukels and Cohen-Kettenis 2011). To be eligible for puberty-suppressing hormones in the Amsterdam

program, adolescents must be age 12 or older, have reached an early stage of pubertal development (Tanner stage 2 or 3), have a history of the onset of gender dysphoria in childhood with increasing symptoms at the start of puberty, have no serious psychiatric comorbidity, have the support of their parents or caregivers, and have the ability to understand the effects of treatment (Kreukels and Cohen-Kettenis 2011).

Suppression of puberty offers significant benefits to adolescents with gender dysphoria. It prevents the unwanted physical changes of puberty and the emotional distress that these changes predictably create, thereby allowing treated adolescents to explore their gender identity concerns and consider future options with greater calmness and less sense of urgency (de Vries and Cohen-Kettenis 2012). It also makes passing in the gender role of the opposite sex much easier if an adolescent decides to proceed with sex reassignment. De Vries et al. (2011b) conducted a prospective follow-up study of the first 70 adolescents offered puberty-suppressing hormones in the Amsterdam program, comparing psychological functioning, gender dysphoria, and body satisfaction before the start of treatment and at its conclusion, when the adolescents became eligible for cross-sex hormone therapy at age 16. The adolescents displayed better psychological functioning after puberty-suppressing treatment and no change in their gender dysphoria or body satisfaction. The latter findings represented the expected (and desired) results, given that normal pubertal development would have been expected to significantly worsen both. All of the treated adolescents subsequently began cross-sex hormone therapy and intended to complete the process of sex reassignment. Initial concerns about the possible medical complications of pubertal suppression have largely been dispelled (Hembree et al. 2009). One significant limitation of the technique, however, is the formidable expense if GnRH analogues are not covered by medical insurance; this is usually the case in the United States (Edwards-Leeper and Spack 2012).

The provision of puberty-suppressing hormones to selected adolescents with gender dysphoria has received widespread endorsement (Edwards-Leeper and Spack 2012; Gooren 2011; Hembree et al. 2009; WPATH 2011), but the technique is not without its critics. Korte et al. (2008) expressed several concerns; they argued that adolescents lack the emotional and cognitive maturity to give meaningful informed consent, that puberty-suppressing hormones might contribute to the persistence of gender dysphoria, and that more effectively addressing the role that parental psychopathology allegedly plays in the etiology of adolescent gender dysphoria might render treatment with puberty-suppressing hormones unnecessary. Perhaps Korte et al.'s (2008) most significant criticism, however, was that the treatment "restricts sexual appetite and functionality and thereby prevents the individual from having age-appropriate (socio-)sexual experiences" (p. 839)—experiences that might theoretically result in a homosexual identity rather than a transsexual one. The latter criticism is especially salient, given the observation by Steensma et al. (2011) that adolescents whose long-standing gender dysphoria desisted between ages 10 and 13 years "reported that their first experience of falling in love and awareness of sexual attraction were factors that resulted in the disappearance of their gender dysphoria" (p. 509). The counterargument, as offered by Kreukels and Cohen-Kettenis (2011), is that

> it seems very unlikely that adolescents who have been through the first stages of puberty and responded to it with an increased intensity of gender dysphoria rather than a (new) enjoyment of their gender of rearing and developing sexuality, will experience a reversal of their GID in the late pubertal stages. (p. 469)

Still, it is not self-evident that reaching age 12 and achieving Tanner stage 2 or 3 pubertal development are sufficient to guarantee that such feelings of sexual attraction and love would already have occurred if they were ever going to. Arrayed against these considerations are the potential harmful consequences of *not* intervening with puberty-suppressing hormones: significant worsening of gender dysphoria and irreversible physical changes that would make passing as a member of the opposite sex much more difficult in adulthood. Given the preponderance of expert opinion in favor of puberty-suppressing hormones for adolescents with gender dysphoria and the increasing numbers of centers offering this treatment, it is likely that researchers and clinicians will soon have a much larger body of data to help clarify the advantages and disadvantages of puberty-suppressing hormones.

Conclusion

Based on several decades of clinical experience with thousands of patients, the value of sex reassignment in the treatment of adults with severe gender dysphoria is not in doubt. At least in adults with the transsexual form of gender dysphoria, careful psychiatric evaluation and treatment with cross-sex hormone therapy, RLE in the desired gender role, and SRS usually result in significant relief of gender dysphoria, improved quality of life, and a low probability of regret. There is less certainty concerning the appropriate treatment of adolescents and children with gender dysphoria. In the case of adolescents whose gender dysphoria began in childhood and persisted through age 12 or 13, there is a small but growing body of evidence that early treatment with puberty-suppressing hormones, followed by hormonal and surgical sex reassignment in adulthood, provides effective treatment. Because most cases of gender dysphoria in childhood desist by the time of adolescence, psychological and social support for the child and his or her family is the generally recommended treatment for children with gender dysphoria.

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PART IX

Disruptive, Impulse-Control, and Conduct Disorders

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Impulse-control disorders (ICDs) are characterized by the recurring inability to abstain from performing a particular action that is harmful either to oneself or others (American Psychiatric Association 2013). ICDs appear to have both neurobiological and environmental origins and are often exacerbated by stress. Typically, impulses are preceded by feelings of tension or arousal, followed by feelings of relief and gratification, and may then be accompanied by guilt or remorse (American Psychiatric Association 2013).

ICDs may represent a spectrum of behaviors, bounded by obsessive-compulsive spectrum disorders on one side and addictive disorders on the other. There is some neurobiological as well as behavioral evidence of links between and among these disorders. Psychosocial and pharmacological treatments emphasize these links, and the fluidity between these disorders is demonstrated by the changes in classification of some former ICDs to the realm of obsessive-compulsive and related disorders and some to addictive disorders (see section "Changes From DSM-IV to DSM-5" below), while several diseases previously categorized as developmental disorders are presumably being relegated to the ICDs because of the marked impulsivity that defines them.

Neurobiology and Pharmacotherapy

It is likely that the wide range of disorders represented under the rubric "impulse-control disorders" are heterogeneous in neurobiological origin and site of action. For this reason, increases in dopaminergic functioning are not able to fully account for this class of disorders. However, it is known that dopamine D_2/D_3 agonists used for the treatment of Parkinson's disease can cause some impulse-control disorders and some addictive dis-

orders (Potenza et al. 2007). As Grant and Odlaug note in Chapter 45, "Kleptomania," "[A]lterations in dopaminergic pathways may produce the feelings of pleasure often associated with [ICDs]. As a result, opioid antagonists which are thought to decrease dopamine neurotransmission in the nucleus accumbens and the corresponding linked motivational neurocircuitry have been… beneficial . . . in dampening excitement and urges." In contrast, neurobiological studies of oppositional defiant disorder (ODD) and conduct disorder (CD) appear to demonstrate lessened fear conditioning, diminished cortisol reactivity to stress, amygdalar underreactivity in response to negative input, and serotonin and noradrenaline levels suggestive of low sensitivity to reprimand. Simultaneously, there appears to be underactivity in the sympathetic nervous system in response to incentives, a phenomenon that is associated with sensation seeking; and diminished dopamine functioning leading to less sensitivity to rewards. Finally, deficits in the paralimbic system may lead to diminished control over emotionally driven behaviors (Matthys et al. 2013). Therefore, in kleptomania, there is a hypersensitivity to pleasure and increased motivation and dopaminergic reaction, and in CD and ODD, there is a hyposensitivity that leads to dampened dopamine responsiveness and a dulling of response to pleasure and averse stimulus, among other factors. These disorders may represent in part, on the one hand, the addictive and compulsive response to enhanced dopamine and, on the other hand, impulsive reward seeking resulting from a paucity of dopamine associated with underarousal and craving.

ICDs may also involve serotonergic, noradrenergic, cholinergic, GABAergic, and glutamatergic dysfunction, in addition to the above-mentioned dopaminergic dysfunction. This is why second-generation antipsychotics, selective serotonin reuptake inhibitors, anticonvulsants, beta-blockers, stimulants, mu opioid antagonists, and benzodiazepines have all been utilized with varying success in treating several of the ICDs, including pyromania, kleptomania, and intermittent explosive disorder (IED) (see, e.g., Chapter 44, "Pyromania"). It may also be why few psychopharmacological agents have been found useful in treating ODD and CD.

Psychosocial Treatments

For ODD, CD, and CD with callous and unemotional specifier, the treatment of choice is psychosocial, with parent management training (PMT) and Triple-P (Positive Parenting Program) emerging as treatments of choice for ODD, and problem-solving skills training (PSST), PMT, multisystemic therapy (MST), cognitive-behavioral therapy (CBT), and in some cases multidimensional treatment foster care (MTFC) emerging as treatments of choice for the two conduct disorders. CBT is thought from case studies to be useful in kleptomania. CBT or fire education safety (FES) were effective psychosocial interventions for pyromania (for further detail, see Chapters 44 and 45 in this volume).

Changes From DSM-IV to DSM-5

DSM-5 includes a new category, "Disruptive, Impulse-Control and Conduct Disorders, that includes ODD, IED, CD, antisocial personality disorder, pyromania, kleptomania, other specified dis-

ruptive, impulse-control, and conduct disorder, and unspecified disruptive, impulse-control, and conduct disorder (American Psychiatric Association 2013). The impulse-control and conduct disorders rubric brings together some disorders from "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence" (ODD and CD) and from "Impulse-Control Disorders Not Elsewhere Classified" (pyromania, kleptomania) in DSM-IV (American Psychiatric Association 1994, 2000). Notably, trichotillomania is now removed from this category and classified as an obsessive-compulsive and related disorder, and pathological gambling is now classified as an addictive disorder.

Comorbidity

Of special note, comorbidity is very common with the ICDs, and attention must be paid to whether the comorbid disorder is treated prior to, along with, or subsequent to treatment of the ICD. For example, stimulant medication improves treatment outcome of attention-deficit/hyperactivity disorder with CD and ODD when used in conjunction with psychosocial therapy, although stimulant use is not a first-line therapy for either of these latter two disorders (see Chapter 40, "Oppositional Defiant Disorder," and Chapter 42, "Conduct Disorder," in this volume). Similarly, Coccaro cites diminished aggression in patients with Cluster B personality disorder patients with IED with divalproex, but not in patients with IED without a Cluster B diagnosis (see Chapter 41, "Intermittent Explosive Disorder"). Naltrexone is considered useful for kleptomania when used to treat the kleptomania alone or when a substance use disorder is also present (see Chapter 45). Finally, selection of treatment for pyromania is almost wholly dependent on comorbidity (see Chapter 44).

Conclusion

There has been considerable change in the domain of the ICDs from DSM-IV to DSM-5 as evidenced by movement of some classic ICDs, such as pathological gambling, to the realm of addictive disorders, and trichotillomania to obsessive-compulsive and related disorders. Further, the domain of ICDs seems to contain subsets, including one consisting of pyromania and kleptomania, that are more similar to addiction and compulsion, and another consisting of impulsive-aggressive conditions such as IED, ODD, CD with or without callous and unemotional specifier. The categorization of disease in the future classification schemes, including the Research Domain Criteria (RDoC), may be influenced more by underlying mechanisms such as brain circuitry than by symptom clusters; treatment modalities may be influenced by neuroimaging and genetic analysis and may involve a more personalized treatment approach. DSM-5 appears to demonstrate movement in this direction, and treatment of the ICDs continues to be a work in progress.

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CHAPTER 40

Oppositional Defiant Disorder

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Oppositional defiant disorder (ODD) is broadly defined as a persistent pattern of defiance and hostility against authority figures (e.g., parents and teachers). A diagnosis of ODD is more common among young children (i.e., ages 3–7 years) manifesting clinically severe levels of disruptive behavior than is conduct disorder (CD). Considerable evidence suggests that ODD often precedes the development of CD in children (e.g., Burke et al. 2010); thus, many researchers consider ODD and CD to be age-related manifestations of a common syndrome, with CD representing a more severe developmental progression of disruptive behavior (Loeber et al. 2009). The DSM-5 criteria for ODD (American Psychiatric Association 2013) are presented in Box 40–1. In contrast to DSM-IV (American Psychiatric Association 1994), DSM-5 organizes symptoms of ODD into three separate, yet interrelated, dimensions: angry/irritable mood, argumentative/defiant behavior, and vindictiveness. Moreover, a comorbid diagnosis of CD alongside ODD is permitted in DSM-5.

Box 40–1. DSM-5 Diagnostic Criteria for Oppositional Defiant Disorder

313.81 (F91.3)

A. A pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness lasting at least 6 months as evidenced by at least four symptoms from any of the following categories, and exhibited during interaction with at least one individual who is not a sibling.

Angry/Irritable Mood

1. Often loses temper.
2. Is often touchy or easily annoyed.
3. Is often angry and resentful.

Argumentative/Defiant Behavior

4. Often argues with authority figures or, for children and adolescents, with adults.
5. Often actively defies or refuses to comply with requests from authority figures or with rules.
6. Often deliberately annoys others.
7. Often blames others for his or her mistakes or misbehavior.

Vindictiveness

8. Has been spiteful or vindictive at least twice within the past 6 months.

Note: The persistence and frequency of these behaviors should be used to distinguish a behavior that is within normal limits from a behavior that is symptomatic. For children younger than 5 years, the behavior should occur on most days for a period of at least 6 months unless otherwise noted (Criterion A8). For individuals 5 years or older, the behavior should occur at least once per week for at least 6 months, unless otherwise noted (Criterion A8). While these frequency criteria provide guidance on a minimal level of frequency to define symptoms, other factors should also be considered, such as whether the frequency and intensity of the behaviors are outside a range that is normative for the individual's developmental level, gender, and culture.

B. The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context (e.g., family, peer group, work colleagues), or it impacts negatively on social, educational, occupational, or other important areas of functioning.
C. The behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder.

Specify current severity:

Mild: Symptoms are confined to only one setting (e.g., at home, at school, at work, with peers).

Moderate: Some symptoms are present in at least two settings.

Severe: Some symptoms are present in three or more settings.

In light of the early development and manifestation of ODD symptoms during childhood, and the setting in which this disorder is typically first characterized (i.e., the family), much of the evidence base concerning the treatment of ODD focuses on family-based interventions. There are currently no specialized interventions targeting the various behavioral or affective dimensions of ODD described in Box 40–1.

Family-Based Interventions

Parent management training (PMT) is the most effective treatment for ODD in young children (Eyberg et al. 2008). PMT is based on coercion theory (Patterson et al. 1992), which outlines social learning–based mechanisms of training in noncompliance in the context of an escalating cycle of coercive parent-child interactions beginning prior to school entry. The proximal causes for entry into the coercive cycle include child temperament (e.g., irritability) and ineffective parenting (e.g., harsh and inconsistent discipline). The goal of PMT is to equip parents with behavior management techniques to improve the quality and consistency of their responding to both negative (e.g., defiance) and positive (e.g., compliance) child behavior. Common elements of evidence-based PMT programs include

1) parent-child relationship building, 2) positive reinforcement (e.g., praise and tangible rewards), and 3) giving clear and effective instructions and implementing noncoercive discipline (e.g., time-outs) (Garland et al. 2008). Intervention is conducted primarily with the parent or parent-child dyad, with relatively less direct therapist-child contact. The envisaged outcome of PMT is a pattern of more positive parent-child interaction leading to increased child prosocial behavior and compliance and less oppositional behavior.

We present a selection of PMT programs as examples of state-of-the-art interventions for young children (ages 3–7 years) with ODD. Descriptions of the clinical procedures used in these programs are widely available (e.g., therapist manuals, videotapes for therapist training, books for parents), and each of the programs has been extensively evaluated; however, space limitations preclude a comprehensive listing of the dozens of PMT programs that are currently available.

The first three PMT programs discussed have their origins in the pioneering work of Constance Hanf (see Reitman and McMahon 2012). They are 1) Helping the Noncompliant Child (HNC; McMahon and Forehand 2003), 2) Parent-Child Interaction Therapy (PCIT; e.g., Brinkmeyer and Eyberg 2003), and 3) The Incredible Years: Early Childhood BASIC Parent Training Program (BASIC; Webster-Stratton 2005). These Hanf-based PMT programs share common features. For instance, each is divided into two phases of treatment. The primary goal in the initial phase is to break the cycle of coercive interactions by establishing a positive, mutually reinforcing parent-child relationship. Parents are taught skills such as attending to and describing their child's appropriate behavior while refraining from using commands, questions, and criticisms. Parents are also instructed to use positive attention, such as praise and physical contact, to encourage child prosocial behavior (e.g., playing calmly), as well as to actively ignore minor inappropriate behaviors (e.g., whining, temper tantrums). In the second phase of treatment, parents are trained in giving clear and effective instructions to their child, and in implementing a systematic time-out procedure to decrease noncompliant behavior. Furthermore, characteristic of all Hanf-based PMT programs, therapists rely on extensive use of modeling and role-play during sessions (in addition to didactic instruction and discussion), as well as home practice assignments and exercises, to teach parents the core skills. HNC and PCIT both use in vivo parent-child interactions for the purpose of coaching parents while they practice new parenting skills during sessions; this component of the programs has been shown to augment the effectiveness of PMT in a meta-analysis (Kaminski et al. 2008).

Two other widely recognized PMT programs for ODD are Triple P—Positive Parenting Program (Triple P; e.g., Sanders et al. 2003) and Parent Management Training—Oregon Model (PMTO; e.g., Patterson et al. 1975). Both programs train parents in a set of parenting skills (e.g., praise, giving clear instructions, time-out) that are similar to those used in the Hanf-based PMT interventions; however, in these latter two programs, the child is not present during sessions and there is no in vivo coaching of parenting skills.

Triple P comprises five levels of intervention, ranging from universal prevention strategies to an intensive and individualized treatment targeting children with severe ODD symptoms. This program was designed for use with parents

of children from birth to age 16 years, although the majority of outcome research has focused on families with young children, ages 2–8 years. Triple P interventions combine PMT strategies with a range of family support materials and services. Level 4 (Standard Triple P) is a more intensive intervention including 8–10 sessions for parents of children with more severe ODD symptoms. This level includes many components of traditional PMT programs, such as a focus on parent-child interaction and training in parenting skills designed to be applicable to a range of problem behaviors.

Patterson et al.'s (1975) treatment manual delineates the PMTO program for preadolescent children (ages 3–12 years). Prior to beginning treatment, parents are given a book (e.g., *Living With Children* [Patterson 1976]) to provide a conceptual background and to facilitate generalization and maintenance. Parents are then taught to pinpoint and track child problem behaviors. Upon mastering these skills, they are then assisted in establishing a positive reinforcement system, using points, tangible reinforcers (e.g., tokens), and social reinforcement (i.e., praise). Over time, tangible reinforcers are faded. After the point system is well established, parents are taught to use a time-out procedure for noncompliance or aggressive behavior. As treatment progresses, parents become increasingly responsible for designing and implementing behavior management programs.

Issues in Intervention Efficacy and Effectiveness

Generalization

There is consistent support for the short-term efficacy of PMT in producing changes in both parent and child behaviors (e.g., Serketich and Dumas 1996), but it is also important to demonstrate the generalization of these effects. For instance, the effects of the various PMT programs discussed have been shown to generalize from the clinic to the home for parent and child behavior; however, generalization of effects from the clinic or home to the school setting is less well established (see McMahon et al. 2006). Moreover, several PMT programs (HNC, PCIT, PMTO, BASIC) demonstrate sibling generalization (e.g., Gardner et al. 2006), and temporal generalization has been demonstrated over follow-up periods of 1–9 years (e.g., Hagen et al. 2011). There also is support for the effectiveness of PMT programs in community settings (e.g., mental health centers, schools) as implemented by staff—such as therapists and counselors—who have received training and supervision in the administration of the intervention (McMahon and Pasalich, in press).

Comparison Studies

Compared with no-treatment and waitlist control groups, PMT has demonstrated significant improvements in child and parent behavior (e.g., Serketich and Dumas 1996). Moreover, increased attention has been focused on the relative efficacy of PMT interventions for ODD compared to other forms of treatment.

For example, in a subset of analyses with children ages 6–12 years, McCart et al.'s (2006) meta-analytic study demonstrated that the mean effect size for PMT (0.45) was higher than the mean effect size for youth cognitive-behavioral therapy (0.23) in decreasing behavior problems. In another meta-analysis comparing PCIT and Triple P, Thomas and Zimmer-Gembeck (2007) reported that although both PMTs had positive effects, the effect sizes were larger for PCIT on some outcomes (e.g., child behavior change).

Mechanisms and Moderation

Several studies demonstrate that changes in parenting behavior mediate the effects of PMT with young children with ODD (e.g., Gardner et al. 2010; Hagen et al. 2011). This is a critical finding that goes to the core of PMT, because improvement in parenting behavior is hypothesized to be the central mechanism by which change in child behavior occurs. In a meta-analytic study examining moderators of PMT, less severe child problem behavior, single-parent status, economic disadvantage, and group-administered (as opposed to individually administered) PMT resulted in poorer child behavior outcomes (Lundahl et al. 2006). Furthermore, among disadvantaged families, individual PMT was associated with more positive child and parent behavioral outcomes than group PMT.

Pharmacological Interventions

There is limited support for the efficacy of pharmacological agents in treating disruptive behavior associated with ODD in children and adolescents. The atypical antipsychotic risperidone may help reduce severe aggression in children and adolescents; however, this medication may cause negative side effects (e.g., weight gain), and its efficacy is yet to be investigated in children under age 5 years (Loy et al. 2012). Moreover, stimulant medication has been shown to treat core symptoms of attention-deficit/hyperactivity disorder (ADHD); however, the recommended first line of treatment for preschoolers with ADHD—with or without comorbid ODD—is PMT (Wolraich et al. 2011). Thus, given the limited evidence for the effectiveness of pharmacotherapy in alleviating severe aggression that may accompany ODD, this intervention should be considered only as a secondary adjunct to PMT, and only for older children and adolescents (Steiner and Remsing 2007).

Conclusion

There is overwhelming support for parent management training as an essential core PMT intervention for reducing ODD symptoms in children ages 3–7 years. Oppositional behavior and defiance in early childhood are robust risk factors for the development of CD in adolescence and antisocial personality disorder in early adulthood; thus, PMT interventions for young children with ODD may have significant preventive effects on these later antisocial outcomes. Given that the potential value of saving a single high-risk youth from a criminal career ranges from $3.2 to $5.5 million (Cohen and Piquero 2009), PMT has great potential to provide a cost-effective means of preventing future delinquency and perhaps even adult criminal activity. In light of recent changes to the conceptualization of ODD in DSM-5 (see Box 40–1), future research is needed to develop and trial novel or modified PMT interventions that are designed to treat specific behavioral or affective dimensions of ODD.

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CHAPTER 41

Intermittent Explosive Disorder

Emil F. Coccaro, M.D.

Pharmacological Treatment

Few double-blind, placebo-controlled clinical trial studies have been published on the treatment of impulsive aggression in subjects with intermittent explosive disorder (IED) diagnosed using the DSM-5 criteria for IED (American Psychiatric Association 2013), which are listed in Box 41–1.

Box 41–1. DSM-5 Diagnostic Criteria for Intermittent Explosive Disorder

312.34 (F63.81)

A. Recurrent behavioral outbursts representing a failure to control aggressive impulses as manifested by either of the following:
   1. Verbal aggression (e.g., temper tantrums, tirades, verbal arguments or fights) or physical aggression toward property, animals, or other individuals, occurring twice weekly, on average, for a period of 3 months. The physical aggression does not result in damage or destruction of property and does not result in physical injury to animals or other individuals.
   2. Three behavioral outbursts involving damage or destruction of property and/or physical assault involving physical injury against animals or other individuals occurring within a 12-month period.

B. The magnitude of aggressiveness expressed during the recurrent outbursts is grossly out of proportion to the provocation or to any precipitating psychosocial stressors.

C. The recurrent aggressive outbursts are not premeditated (i.e., they are impulsive and/or anger-based) and are not committed to achieve some tangible objective (e.g., money, power, intimidation).

D. The recurrent aggressive outbursts cause either marked distress in the individual or impairment in occupational or interpersonal functioning, or are associated with financial or legal consequences.
E. Chronological age is at least 6 years (or equivalent developmental level).
F. The recurrent aggressive outbursts are not better explained by another mental disorder (e.g., major depressive disorder, bipolar disorder, disruptive mood dysregulation disorder, a psychotic disorder, antisocial personality disorder, borderline personality disorder) and are not attributable to another medical condition (e.g., head trauma, Alzheimer's disease) or to the physiological effects of a substance (e.g., a drug of abuse, a medication). For children ages 6–18 years, aggressive behavior that occurs as part of an adjustment disorder should not be considered for this diagnosis.

Note: This diagnosis can be made in addition to the diagnosis of attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder, or autism spectrum disorder when recurrent impulsive aggressive outbursts are in excess of those usually seen in these disorders and warrant independent clinical attention.

The first studies in this area reported a reduction in impulsive aggressive behavior in fluoxetine-treated personality-disordered patients with IED (diagnosed using the research criteria that have become DSM-5 IED criteria) (Coccaro and Kavoussi 1997; Coccaro et al. 2009). Fluoxetine was begun at 20 mg/day and increased to 40 mg/day and then to 60 mg/day every 4 weeks if the aggression outcome measure was not reduced in magnitude by 75%.

Ultimately, the mean dosage of fluoxetine at endpoint was 30 mg/day po, with 58% of subjects taking 20 mg/day, 30% taking 40 mg/day, and 12% taking 60 mg/day (Coccaro et al. 2009). The reduction of verbal aggression was the most notable result of treatment with fluoxetine compared with placebo. Although a difference in physical aggression was not noted for patients taking fluoxetine versus those given placebo, there was no difference in the degree of lifetime physical aggression between subjects who did and those who did not respond to fluoxetine, suggesting that given a longer observational period, physical aggression would also be reduced by fluoxetine. Plasma levels of fluoxetine and its metabolites did not differ between responders and nonresponders, indicating that the latter group did not respond despite apparently therapeutic levels of fluoxetine having been achieved.

Most importantly, this study confirmed, in a prospective fashion, that fluoxetine does not increase impulsive aggressive behavior, especially in aggressive individuals. In addition, fluoxetine treatment was associated with full remission of Criterion A for IED in 29% of subjects and partial remission in 17%, indicating that even though fluoxetine can reduce impulsive aggression, substantial improvement may be limited to less than 50% of all subjects with IED who are treated with fluoxetine. Most adverse events were mild in severity, with the most commonly reported events being sexual dysfunction (26%), followed by sleep disturbance (22%), nausea/vomiting (22%), and jitteriness/restlessness (22%) (Coccaro et al. 2009).

In a study by Coccaro et al. (1997), pretreatment central serotonergic system function was directly related to the anti-aggressive effect of fluoxetine at endpoint, indicating that the more functional

the postsynaptic serotonin receptor, the larger the antiaggressive response to fluoxetine. In another study, pretreatment levels of neuroticism correlated inversely with the antiaggressive response to fluoxetine (Phan et al. 2011), suggesting that one mechanism by which fluoxetine may reduce impulsive aggression is by reducing negative emotionality. The basic treatment response finding was replicated in two other studies with fluoxetine, which involved subjects with histories of impulsive aggression (Silva et al. 2010) or perpetrators of intimate partner violence (George et al. 2011), although neither study used entry criteria exactly like those appearing in DSM-5. In the first study, the presence of the s allele for the 5-HT transporter promoter polymorphism was associated with a poorer response to fluoxetine (Silva et al. 2010). This suggests that a reduction in presynaptic 5-HT transporters limits the ability for fluoxetine to enhance 5-HT function because there are fewer 5-HT transporters to inhibit and to allow for increases in synaptic 5-HT. This finding is also consistent with reports that 5-HT transporter levels are inversely related to aggression both in platelets (Coccaro et al. 2010) and in brain (Frankle et al. 2005).

Another study found that divalproex reduced impulsive aggression in patients with DSM-IV Cluster B personality disorders and IED (diagnosed using the research criteria that have become DSM-5 IED criteria) (Hollander et al. 2003). The design was similar to those of the first fluoxetine studies (Coccaro and Kavoussi 1997; Coccaro et al. 2009), and in subjects who were receiving divalproex, the mean dosage at endpoint was 1,567 mg/day, with a trough blood level of 64.2 μg/mL. Whereas IED subjects (regardless of personality disorder) who were treated with divalproex demonstrated no reduction in aggression compared with subjects treated with placebo, IED subjects with Cluster B personality disorders did display a significant reduction in total aggression, verbal aggression, aggression against property, and aggression against others over the last 4 weeks of the 12-week trial (all Ps<0.05). Most adverse events were mild or moderate in severity, with the most commonly reported events being somnolence (29%), headache (24%), and nausea (20%). Specific treatment-emergent adverse events for divalproex were statistically significant for asthenia, depression, increased appetite, increases in serum glutamic-pyruvic transaminase and serum glutamic-oxaloacetic transaminase, nausea, nervousness, and tremor.

Two other studies examined whether oxcarbazepine or levetiracetam could reduce impulsive aggression in subjects with IED diagnosed using the research criteria that were ultimately adopted for DSM-5 IED. In a 10-week study using orally administered oxcarbazepine, oxcarbazepine was started at a dosage of 150 mg/day, and the dosage was increased every 2–4 days in the first 4 weeks by 150–300 mg/day (in two daily doses), to a minimum of 1,200 mg/day and a maximum of 2,400 mg/day (Mattes 2005). The mean dosage was 1,500 (±630) mg/day. Overall, antiaggressive effects were seen for both verbal aggression and for aggression against objects. Adverse events were generally minor and consistent with what would be expected within this dose range. The study using levetiracetam (Mattes 2008) had the same design but demonstrated no antiaggressive effect for this agent at a mean dosage

of 1,738 (±1,028) mg/day. This negative finding suggests that not all anticonvulsive agents possess antiaggressive properties.

Cognitive-Behavioral Therapy

One published study has been done of a cognitive-behavioral therapy (CBT) intervention versus a wait-list control condition in patients with IED diagnosed with the research criteria that were subsequently adopted for DSM-5 IED (McCloskey et al. 2008). The intervention was 12 sessions long and included relaxation training, cognitive restructuring, and coping skills training. It was adapted from an 8-session CBT protocol for the treatment of anger by Deffenbacher and McKay (2000). In the McCloskey et al. study, impulsive aggression, anger, and hostile automatic thoughts were all significantly reduced by the CBT group (regardless of whether the CBT was delivered in individual or group format) compared with the wait-list control group. This CBT intervention was efficacious regardless of whether subjects displayed high or moderate levels of aggression. In addition, the overall antiaggressive response to this CBT intervention was similar to that of fluoxetine in IED subjects (Coccaro et al. 2009), suggesting that a combination of the two interventions may be even more effective than one alone.

Conclusion

Although IED has been in DSM since 1980 (DSM-III), very few controlled treatment studies of patients with this diagnosis have been published. Pharmacological agents that have been reported to reduce impulsive aggressive behavior in IED subjects include, broadly speaking, selective serotonin reuptake inhibitors and mood stabilizers. CBT may also be effective in treating IED, and the combination of medication and CBT is likely to be more effective, although there are no empirical data yet to support this claim.

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CHAPTER 42

Conduct Disorder

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Conduct disorder (CD) is characterized by a repetitive and persistent pattern of behavior that violates the rights of others or major age-appropriate societal rules (see Box 42–1). Although the current chapter is designed to provide an overview of empirically supported treatments for CD, relatively few psychosocial interventions have been explicitly designed for children diagnosed with CD. This review therefore focuses on interventions shown to be efficacious in samples that contain a significant proportion of youth who meet criteria for CD, and those designed for youth exhibiting severe criminal behavior. All of the psychosocial treatments reviewed have appeared on vetted lists of empirically supported programs for antisocial and delinquent youth (Eyberg et al. 2008; Office of the Surgeon General 2001). Pharmacological interventions that have been shown to be effective in reducing CD symptoms in placebo-controlled trials are also discussed. Research on the treatment of youth who meet criteria for CD with limited prosocial emotions is discussed in Chapter 43, "With Limited Prosocial Emotions Specifier for Conduct Disorder."

Box 42–1. DSM-5 Diagnostic Criteria for Conduct Disorder

A. A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of at least three of the following 15 criteria in the past 12 months from any of the categories below, with at least one criterion present in the past 6 months:

Aggression to People and Animals

1. Often bullies, threatens, or intimidates others.
2. Often initiates physical fights.
3. Has used a weapon that can cause serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun).
4. Has been physically cruel to people.
5. Has been physically cruel to animals.
6. Has stolen while confronting a victim (e.g., mugging, purse snatching, extortion, armed robbery).
7. Has forced someone into sexual activity.

Destruction of Property

8. Has deliberately engaged in fire setting with the intention of causing serious damage.
9. Has deliberately destroyed others' property (other than by fire setting).

Deceitfulness or Theft

10. Has broken into someone else's house, building, or car.
11. Often lies to obtain goods or favors or to avoid obligations (i.e., "cons" others).
12. Has stolen items of nontrivial value without confronting a victim (e.g., shoplifting, but without breaking and entering; forgery).

Serious Violations of Rules

13. Often stays out at night despite parental prohibitions, beginning before age 13 years.
14. Has run away from home overnight at least twice while living in the parental or parental surrogate home, or once without returning for a lengthy period.
15. Is often truant from school, beginning before age 13 years.

B. The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.

C. If the individual is age 18 years or older, criteria are not met for antisocial personality disorder.

Specify whether:

312.81 (F91.1) Childhood-onset type: Individuals show at least one symptom characteristic of conduct disorder prior to age 10 years.

312.82 (F91.2) Adolescent-onset type: Individuals show no symptom characteristic of conduct disorder prior to age 10 years.

312.89 (F91.9) Unspecified onset: Criteria for a diagnosis of conduct disorder are met, but there is not enough information available to determine whether the onset of the first symptom was before or after age 10 years.

Specify if:

With limited prosocial emotions: To qualify for this specifier, an individual must have displayed at least two of the following characteristics persistently over at least 12 months and in multiple relationships and settings. These characteristics reflect the individual's typical pattern of interpersonal and emotional functioning over this period and not just occasional occurrences in some situations. Thus, to assess the criteria for the specifier, multiple information sources are necessary. In addition to the individual's self-report, it is necessary to consider reports by others who have known the individual for extended periods of time (e.g., parents, teachers, co-workers, extended family members, peers).

Lack of remorse or guilt: Does not feel bad or guilty when he or she does something wrong (exclude remorse when expressed only when caught and/or facing punishment). The individual shows a general lack of concern about the negative

consequences of his or her actions. For example, the individual is not remorseful after hurting someone or does not care about the consequences of breaking rules.

Callous—lack of empathy: Disregards and is unconcerned about the feelings of others. The individual is described as cold and uncaring. The person appears more concerned about the effects of his or her actions on himself or herself, rather than their effects on others, even when they result in substantial harm to others.

Unconcerned about performance: Does not show concern about poor/problematic performance at school, at work, or in other important activities. The individual does not put forth the effort necessary to perform well, even when expectations are clear, and typically blames others for his or her poor performance.

Shallow or deficient affect: Does not express feelings or show emotions to others, except in ways that seem shallow, insincere, or superficial (e.g., actions contradict the emotion displayed; can turn emotions "on" or "off" quickly) or when emotional expressions are used for gain (e.g., emotions displayed to manipulate or intimidate others).

Specify current severity:

Mild: Few if any conduct problems in excess of those required to make the diagnosis are present, and conduct problems cause relatively minor harm to others (e.g., lying, truancy, staying out after dark without permission, other rule breaking).

Moderate: The number of conduct problems and the effect on others are intermediate between those specified in "mild" and those in "severe" (e.g., stealing without confronting a victim, vandalism).

Severe: Many conduct problems in excess of those required to make the diagnosis are present, or conduct problems cause considerable harm to others (e.g., forced sex, physical cruelty, use of a weapon, stealing while confronting a victim, breaking and entering).

Psychosocial Treatments

Problem-Solving Skills Training With Parent Management Training

Kazdin's (2010) problem-solving skills training (PSST) with parent management training (PMT) program was initially designed for children ages 5–13 years who meet criteria for oppositional defiant disorder (ODD) or CD. PSST is mainly composed of 12 weekly sessions (30–50 minutes each) designed to teach and reinforce strategies for effectively dealing with interpersonal conflicts. As part of these sessions, children are taught to objectively evaluate problem situations, develop prosocial goals, and generate alternative solutions to meet their goals. Children initially practice these skills using hypothetical conflict situations that may arise in the settings where they are having the most problems. Children are then assigned "super-solver" tasks in which they apply these strategies to real-life situations. The PMT portion of the intervention involves a core set of 12 weekly sessions (45–60 minutes each) designed to teach parents to use behavioral principles to modify problematic child behavior. Topics covered include the appropriate use of parenting techniques such as positive reinforcement, time-out, verbal reprimands, negotiation, and behavioral contracting. Therapists also help parents identify explicit school goals, which are monitored using a home-school behavioral report

card system, and children are rewarded for achieving specific behavioral milestones.

Randomized controlled trials have found that PSST and PMT are superior to nondirective relationship therapy in reducing antisocial behavior and improving prosocial skills and overall school adjustment, with positive behavioral gains remaining at 1-year posttreatment (Kazdin 2010). Although PSST and PMT can be administered in isolation, implementing both programs together tends to produce the greatest behavioral gains (Kazdin et al. 1992). However, PMT should be implemented whenever possible with children diagnosed with ODD or CD, because it has been shown to be more effective than cognitive-behavioral therapies such as PSST for treating behavior problems in children ages 6–12 (McCart et al. 2006). Although certification workshops are available to help disseminate Kazdin's PMT/PSST to community therapists, relatively few therapists have undergone the certification process either (see http://childconductclinic.yale.edu/certified-clinicians), and no published studies have examined the efficacy of PMT/PSST in community-based clinic settings.

Multisystemic Therapy

Multisystemic therapy (MST) was originally designed as an intensive family- and community-focused treatment for seriously delinquent adolescents ages 11–17 (Henggeler 2011). The intervention emphasizes the interaction between adolescents and the multiple environmental systems that influence their behavior (e.g., peers, family, school, community). MST is delivered in the family's natural environment and can include a combination of different treatment approaches (e.g., PMT, family therapy, school consultation) tailored to the needs of the family. Treatment strategies are developed in collaboration with family members after identifying factors that help maintain the adolescents' deviant behavior. Methods for overcoming barriers to positive behavior change are also discussed in session. Clinicians are guided by a set of nine MST principles, which include concepts such as focusing on strengths and encouraging responsible behavior. MST therapists are available 24 hours a day, 7 days a week. Families typically receive 40–60 hours of clinical contact over the course of 3–5 months.

Several randomized trials have found that adolescent offenders who receive MST exhibit lower rates of delinquent behavior, substance use, recidivism, and incarceration after treatment compared with teens receiving standard community care (Henggeler and Sheidow 2012). Sawyer and Borduin (2011) found that seriously delinquent juveniles who received MST continued to exhibit lower rates of recidivism relative to adolescents assigned to individual therapy 21.9 years after treatment initiation. MST's positive influence on antisocial behavior appears to be due in part to the program's ability to improve family relations, increase the use of positive discipline techniques, and reduce deviant peer group affiliation (Henggeler 2011; Henggeler and Sheidow 2012). MST has now been disseminated to more than 500 international agencies, resulting in a number of independent studies examining the effectiveness of the program in "real-world" settings. Results from some of these studies have been less impressive, with small or nonsignificant treatment effects on externalizing problems when MST is compared with usual care, which may be due in part to reduced treatment adherence by community-based therapists (Henggeler 2011; Littell et al. 2005).

Multidimensional Treatment Foster Care

Multidimensional treatment foster care (MTFC) was designed as an alternative to traditional group care for delinquent adolescents (ages 12–17) removed from their homes (Chamberlain 2003). This multicomponent intervention places the youth with a community-based foster family, where contingencies governing the youth's behavior are modified through consultation with a comprehensive treatment team. Each foster family is assigned a program supervisor, foster parent consultant, behavior support specialist, family therapist, parent daily report caller, and consulting psychiatrist to assist with program implementation. Adolescents earn privileges through a level system by following a daily program of scheduled activities and fulfilling behavioral expectations. Program staff provide around-the-clock support for crisis management, assist in creating a school-based support plan, and provide individualized skills coaching as necessary. The adolescents' future guardian(s) assists in treatment planning, engages in family therapy, and begins applying newly learned parenting skills during home visits. Cases are followed for 1–3 months after reunification to assist with managing problems as they arise.

Studies using randomized and matchcontrol designs have found that delinquent adolescents assigned to receive MTFC are more likely to complete their placement, have fewer arrests and days of incarceration, and have lower self-reported delinquency and substance use compared to adolescents in standard group care (Chamberlain 2003; Fisher and Gilliam 2012). Reduced affiliation with deviant peers and improvements in family management practices seem to account for MTFC's positive impact on delinquent behavior (Eddy and Chamberlain 2000; Henggeler and Sheidow 2012), and have been observed for up to 2 years following treatment initiation (Chamberlain 2003; Fisher and Gilliam 2012). Widespread dissemination of MTFC is currently being supported by TFC Consultants, Inc., and a growing number of independent studies evaluating the efficacy of the program are under way (Chamberlain 2003). Although some of these studies suggest that MTFC improves placement stability, reductions in delinquent behavior tend to dissipate once youths leave the program (Biehal et al. 2011; Hansson and Olsson 2012).

Functional Family Therapy

Functional family therapy (FFT) is an intervention for delinquent adolescents (ages 11–17) and their families that combines principles of family systems theory with cognitive-behavioral approaches (Sexton 2010). FFT consists of three intervention phases: 1) engagement/motivation, 2) behavior change, and 3) generalization. During the engagement/motivation phase, the therapist begins establishing a strong therapeutic alliance with the family, addresses maladaptive family beliefs to increase expectations for change, and reduces negativity and blaming within the family system. The behavior change phase involves implementing an individualized treatment plan to improve family functioning, which may include building relational skills, enhancing positive parenting, and reducing maladaptive familial interactions. Finally, the generalization phase is designed to improve the family's ability to competently influence the systems in which it is embedded (e.g., school, community, justice system) in order to maintain positive behavioral change. Families in FFT typically attend 12 treatment sessions over the course of 3–4 months.

Early studies using randomized and nonrandom designs found that FFT improved family functioning and reduced recidivism in delinquent adolescents relative to alternative treatments and typical probation services (Barton et al. 1985; Klein et al. 1977). However, some randomized trials with substance-abusing adolescents failed to find evidence that FFT is superior to alternative treatments in reducing externalizing problems (Henggeler and Sheidow 2012). In addition, studies examining the mechanisms through which FFT produces positive behavioral change are still lacking. Under the direction of FFT LLC, the intervention has now been disseminated to over 300 agencies worldwide (see http://www.fftinc.com/index.html). Similar to findings with MST and MTFC, studies conducted in community settings as part of these dissemination efforts have produced less consistent results. For example, a large randomized efficacy trial (N=914) found that FFT did not produce reductions in recidivism among delinquent adolescents relative to standard probation (Sexton and Turner 2010). When analyses were restricted to FFT therapists rated as highly adherent to the treatment model, significant reductions in felony recidivism were found. In contrast, adolescents under the care of FFT therapists with low adherence ratings actually had higher rates of felony recidivism.

Pharmacotherapy

No large randomized placebo-controlled studies with extended follow-ups have evaluated the efficacy of medication in treating CD symptoms. However, some evidence suggests that the atypical antipsychotic risperidone is efficacious in acutely reducing aggressive behavior among youths ages 5–18 with CD (particularly those with low intelligence), although side effects such as lethargy, headaches, and weight gain are a concern (Loy et al. 2012). Methylphenidate may also help reduce aggression in youths with comorbid attention-deficit/hyperactivity disorder (ADHD) and CD (Pappadopulos et al. 2006), with decreased appetite and insomnia being the most commonly reported side effects. In general, psychosocial interventions are recommended as the first line of treatment for youths with CD, with stimulant medications being used when comorbid ADHD is present, and risperidone being considered as a potential adjunct when severe aggression remains.

Conclusion

Although the evidence supporting various interventions targeting symptoms of conduct disorder has grown over the past several decades, many youths continue to exhibit significant behavioral impairments at the end of treatment and positive behavioral gains tend to erode over time. In the future, it will be important to develop more systematic methods for tailoring treatments to the unique characteristics of children and families, based on the developmental mechanisms underlying their conduct problems, in order to optimize treatment efficacy. In addition, booster sessions may be necessary to help sustain positive behavioral gains over extended periods of time. It will also be important to develop more effective means for disseminating interventions to real-world settings, particularly because many interventions show diminished effects when transported into the community, likely due in part to reductions in treatment adherence.

Recommended Readings

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CHAPTER 43

With Limited Prosocial Emotions Specifier for Conduct Disorder

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Children whose presentations meet DSM-5 criteria for the "with limited prosocial emotions" specifier for conduct disorder (CD) present with two or more of the following characteristics over at least 12 months and in multiple relationships or settings: lack of remorse or guilt, callousness–lack of empathy, lack of concern about performance in important activities, and shallow or deficient affect (American Psychiatric Association 2013; see Chapter 42, "Conduct Disorder"). Decades of research have been devoted to understanding how these so-called callous-unemotional (CU) traits develop among youths, but knowledge is limited on how to best treat this population. Findings are mixed regarding whether treatment improves conduct problems among youths with CU traits; however, there is converging evidence to suggest that CU traits can be treated with psychosocial interventions. Children with conduct problems and CU traits (hereafter referred to as CP+CU) tend to exhibit a reduced sensitivity to punishment when they have already learned that a behavior is reinforcing and tend to have problems processing others' emotions, which may complicate treatment efforts (see Frick et al. 2014).

Psychosocial Treatments

To adequately discuss the range of potentially effective treatments for children with CP+CU, we need to consider research conducted with youths with a

broader range of conduct problems than those who would meet diagnostic criteria for CD. Of importance, no treatment studies—or randomized controlled trials (RCTs) in particular—have explicitly targeted specifically children with CP+CU.

Parent Management Training/Behavioral Therapy

A well-replicated finding is that the conduct problems of children with CU traits are less strongly associated with some negative parenting practices (i.e., harsh/inconsistent discipline) compared with children without CU traits (e.g., Wootton et al. 1997). In line with these findings, there is some evidence that traditional parent management training (PMT) interventions are less effective at treating conduct problems among children with CU traits than they are for children without these traits. For example, Hawes and Dadds (2005) found that parents of boys (mean age=6.29 years) with higher levels of CU traits were more likely to rate the discipline component (i.e., time-out) of a manualized PMT program as ineffective at reducing their children's conduct problems during treatment relative to parents whose children had oppositional defiant disorder (ODD) alone. Furthermore, in this study, CU traits predicted a posttreatment diagnosis of ODD. Moreover, in a summer treatment program for children with attention-deficit/hyperactivity disorder (ADHD), Waschbusch et al. (2007) found that conduct problems in children (ages 7–12 years) with versus without CU traits showed less improvement after behavior therapy. Children who score high on CU traits were also observed to be less compliant to the time-out component of the intervention (Haas et al. 2011). Another study of adolescents (ages 11–17 years) involved with the justice system found that those scoring high on CU traits were more likely to engage in violent behavior during the course of functional family therapy and demonstrated lower youth- and parent-reported perceptions of improvement (White et al. 2013). They also showed the highest levels of conduct problems, aggression, and emotional symptoms prior to treatment, which were significantly reduced but remained higher than youths with low CU traits at posttreatment.

Some evidence suggests that reward-based parenting strategies (e.g., descriptive praise) might be particularly effective in reducing conduct problems in children with CU traits. For instance, Hawes and Dadds (2005) found that CU traits were not significantly associated with parents' perceptions of the ineffectiveness of reward-based strategies as they were for time-out. This research suggests that existing empirically supported interventions for conduct problems may be adapted or modified to better fit the individualized needs of children with CU traits by emphasizing reward-based strategies. A case study designed to test this possibility reported that adapting parent-child interaction therapy (PCIT; Zisser and Eyberg 2010) by implementing an adjunctive token economy system to modify behaviors was successful at reducing conduct problems to below clinically significant levels in a young boy with marked CU traits (Kimonis and Armstrong 2012a). However, standard PCIT (without adaptation) was also effective at reducing conduct problems to subclinical levels in very young children (mean age=3.87 years) with CU features, albeit not to the same levels as children

scoring low on these traits (Kimonis et al. 2014).[1]

Notwithstanding their reduced effectiveness for treating the conduct problems of children with CU traits, PMT interventions do appear to improve the CU traits themselves, with medium to large effect sizes reported. For example, one RCT found that children ages 4–9 years diagnosed with ODD/CD recruited from domestic violence shelters whose mothers received PMT and supportive therapy exhibited greater reductions in CU traits compared with those who received services as usual in the community (McDonald et al. 2011). Furthermore, improvements in mothers' harsh and inconsistent parenting partly accounted for the reductions in levels of CU traits. Similarly, Hawes and Dadds (2007) found lower levels of CU traits at 6 months posttreatment for a subset of their 2005 study sample (Hawes and Dadds 2005).

It is possible that improving the affective quality of the parent-child relationship by increasing parental involvement and warmth might further lower CU traits. Longitudinal studies suggest that positive parenting reduces CU traits across time (e.g., Pardini et al. 2007). Specifically, parenting styles promoting greater attachment security—namely, parental warmth and sensitive responding to child emotion—are believed to be critical to socializing and fostering conscience development among children with the fearless and uninhibited temperament believed to underlie CU traits, and also to reducing the risk of further development of these traits (Kochanska 1997). An RCT of Israeli children (ages 2.6–5 years) with significant conduct problems that incorporated strategies for improving aspects of the parent-child relationship (e.g., warmth, communication skills) within a PMT program, and that mandated participation by both parents and addressed co-parenting, found that CU traits improved posttreatment compared with those of control subjects (Somech and Elizur 2012). A similar intervention that adapted PCIT for children with CU traits (Kimonis and Hunt 2012) by incorporating reward-based strategies is currently being pilot tested, with preliminary findings suggesting that it is effective at reducing conduct problems in young clinic-referred children with CU traits (analytic details available on request). Dadds and Rhodes (2008) suggest that instructing parents to calmly establish close eye contact and physical proximity to redirect the child's attention to the emotional salience of the situation might improve the chances of positive outcomes with time-out. Taken together, these findings suggest that traditional PMT interventions delivered within the context of a warm and supportive parent-child relationship may prevent or ameliorate the development of CU traits (Pasalich et al. 2011).

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) may be particularly useful for older youths with CP+CU in settings where parents may be unavailable, such as in juvenile justice settings. Researchers are in the process of developing individualized approaches to treating incarcerated adolescents with symptom criteria aligned

[1]These findings require replication in a sample of nondelayed children with conduct problems because subjects in this study were either developmentally delayed or at risk for developmental delay due to premature birth.

with DSM-5's CU specifier to CD; however, the effectiveness of these approaches for reducing CU traits is not well established (Salekin et al. 2012a). For example, among a sample of incarcerated youths (mean age=14.67 years), a 10- to 12-week group-based positive psychology intervention (i.e., mental models intervention designed to increase motivation and raise positive emotion) used in combination with behavioral strategies (i.e., staff use of shaping and positive over negative reinforcement) had a small, nonsignificant effect on reducing CU traits (Salekin et al. 2012b). Although the researchers did not examine to what extent treatment influenced conduct problems, they suggest that changes in youths' cognitive skill sets may be a protective resource against making maladaptive choices. Incarcerated youths present a unique treatment challenge because their CU traits are modestly associated with treatment noncompliance, poor attendance, and higher dropout rates (see Salekin 2010 for a review). Salekin (2010) identified further areas of concern for therapists, including poor motivation to change, manipulation/deceit, and an inability to form lasting attachments or experience deep emotions.

Interventions previously tested for youths with CP+CU are generally limited in that they fail to address core deficits in emotional reactivity and understanding of others' distress cues, which distinguish these youths from other youths with conduct problems. Emotional deficits among youths with CP+CU are believed to be central to their poor moral development (Blair 1999). One line of study attributes poor emotion recognition to problematic allocation of attention to critically salient environmental cues—namely, failing to focus on the eye region of the face when processing fearful expressions as determined by eye tracking (Dadds et al. 2008). When youths with CU traits were instructed to attend to the eyes of stimulus faces, their deficits in fear recognition ameliorated, suggesting that altering the attentional focus of children with CU traits may, at least temporarily, modify impairments in emotion recognition (Dadds et al. 2006, 2008).

Whether or not redirecting attention to the eye region of the face will affect CU traits and conduct problems is an empirical question because there is no longitudinal evidence to suggest that eye-gaze deficits are associated with the stability of CU traits or conduct problems over time. However, in an RCT of largely male youths referred for emotional and behavioral problems (ages 6–16 years), those with elevated CU traits showed significant improvements in affective empathy and conduct problems following computerized emotional recognition training compared with a treatment-as-usual (TAU) PMT intervention (Dadds et al. 2012). Emotional training involved studying images of various human emotional expressions and then discussing them with parents during homework activities. However, there was no evidence that improvements in emotion recognition and affective empathy accounted for the positive impact that the intervention had on conduct problems in children high on CU traits. Also, in a follow-up to Kimonis and Armstrong's (2012a) case study (discussed in the subsection "Parent Management Training/Behavioral Therapy" earlier in this chapter), an adjunctive emotional skills building module was effective at increasing empathy in a child with severe CP+CU. This module, called Coaching and Rewarding Emotional Skills, teaches children emotional skills (e.g., recognition, affective perspective taking) using a variety of parent-child

activities drawn from empirically validated interventions for developing emotional skills in young children and in children with autism spectrum disorders (Kimonis and Armstrong 2012b). These findings highlight the promising potential of empirically based adjunctive interventions for addressing core emotional deficiencies in children with CP+CU.

Pharmacotherapy

Stimulant medication may have potential for improving conduct problems in children with co-occurring ADHD and CU traits. Waschbusch et al. (2007) found that treatment differences between children with CP+ADHD, with and without CU traits, largely disappeared when using a combination of behavior therapy and stimulant medication. The mechanism by which stimulants may benefit children with CU traits remains unclear.

Multimodal/ Multidimensional Interventions

Interventions for youths with severe conduct problems are most successful when they are both comprehensive and individualized (Frick 2001). One such modular treatment employing PMT, school-based contingency management, family therapy, CBT, social skills training, ADHD medication, and/or crisis management interventions—delivered on the basis of the child's individual needs—significantly reduced CU traits across a 3-year follow-up period among clinically referred children (ages 6–11 years) diagnosed with ODD or CD (Kolko et al. 2009). A second study comparing this treatment approach with TAU found that CU traits did not significantly predict poorer posttreatment outcomes across a 3-year follow-up among clinically referred children with ODD or CD, after controlling for severity of conduct problems (Kolko and Pardini 2010).

Another multimodal intervention study found that adolescent offenders with CU traits who were treated using reward-oriented contingency management strategies that targeted the self-interests of the adolescent and also taught empathy skills were less likely to reoffend over a 2-year follow-up period than were those who underwent TAU in the same correctional facility (Caldwell et al. 2006). However, other studies examining multimodal interventions have reported that treatment effects are poorer for children with high CU traits compared with children with low CU traits (Stadler et al. 2012). Future research is needed to establish whether empirically validated multimodal treatments for severe conduct problems, such as multisystemic therapy and multidimensional treatment foster care (Henggeler and Sheidow 2012), are effective at reducing conduct problems and CU traits in these youths.

Conclusion

Despite a history of psychotherapeutic pessimism (see Salekin 2010), there is encouraging evidence that the callous-unemotional traits of children with CP + CU are modifiable; however, these youths tend to receive less benefit from traditional interventions than do their non-CU counterparts, particularly with respect to conduct problems outcomes. Future research should examine whether

other empirically supported treatment approaches (see Chapter 40, "Oppositional Defiant Disorder") are effective at reducing conduct problems, particularly when they are tailored to meet the specific treatment needs of youths with CU traits. Improving treatment outcomes for children with CP+CU may be accomplished by 1) further emphasizing techniques to strengthen the parent-child relationship (i.e., warmth, responsiveness); 2) emphasizing positive reinforcement (i.e., praise, token economy) over punishment to modify behaviors; 3) prescribing stimulant medication when there is comorbid ADHD; and 4) focusing on enhancing empathy and emotional responsiveness in the child.

A rich body of basic science findings has the potential to inform the development of novel behavioral, cognitive, and biological interventions for children with CP+CU, which are critically needed to address the unique emotional deficits that are believed to contribute to their poor moral socialization. For example, future research may examine whether attentional bias retraining therapy diminishes core emotional deficits for youths with CP+CU by increasing their attention to cues of fear or sadness in others or to salient aspects of these expressions given its success in treating anxiety disorders (see Hakamata et al. 2010). Attentional retraining uses subtle reward cues to behaviorally shape and modify biases in attention and may be used adjunctively with traditional interventions. Furthermore, longitudinal research is desperately needed to establish whether reported improvements in treatment outcomes persist across extended periods of time. Each of these advances is critical given evidence for particularly severe, stable, and aggressive patterns of antisocial behavior among youths with CP+CU.

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CHAPTER 44

Pyromania

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Pyromania is a disorder in which the individual sets fires to reduce tension or to obtain and then reduce affective arousal. It can cause the sufferer significant distress, shame, and dysfunction (Grant and Kim 2007) and characteristically has great psychological comorbidity (Hollander et al. 2008; Grant and Kim 2007). Pyromania is distinguished from *fire setting*, which is a behavior, and *arson*, which is a criminal act (Burton et al. 2012). Most fire-setting behavior is not related to pyromania. In one study of 90 arsonists, only 3.3% had pyromania; several other subjects met the criteria for pyromania only when setting fires while intoxicated (Lindberg et al. 2005).

In DSM-5 (American Psychiatric Association 2013), pyromania is one of the disruptive, impulse-control, and conduct disorders. Impulse-control disorders (ICDs) are characterized by failure to resist an impulse, resulting in a behavior that could impose harm on the individual performing the act or on others. The individual has a sense of arousal or tension just before engaging in the act, and experiences pleasure and tension release at the time of the act (Hollander et al. 2008). Principles of personal responsibility for fire setting may impact how patients with pyromania are treated. Pyromania is characterized in DSM-5 by six criteria (see Box 44–1) that include impulsive, repetitive, and intentional fire setting with no ulterior reward from the fire itself. Research regarding treatment of pyromania is severely limited because epidemiological data are culled from arson literature through the justice system, whereas fires set by persons with pyromania may be legal.

Box 44–1. DSM-5 Diagnostic Criteria for Pyromania

312.33 (F63.1)

A. Deliberate and purposeful fire setting on more than one occasion.
B. Tension or affective arousal before the act.
C. Fascination with, interest in, curiosity about, or attraction to fire and its situational contexts (e.g., paraphernalia, uses, consequences).

D. Pleasure, gratification, or relief when setting fires or when witnessing or participating in their aftermath.
E. The fire setting is not done for monetary gain, as an expression of sociopolitical ideology, to conceal criminal activity, to express anger or vengeance, to improve one's living circumstances, in response to a delusion or hallucination, or as a result of impaired judgment (e.g., in major neurocognitive disorder, intellectual disability [intellectual developmental disorder], substance intoxication).
F. The fire setting is not better explained by conduct disorder, a manic episode, or antisocial personality disorder.

Pyromania peaks in adolescence, but may begin in early childhood, and often precedes other disorders and comorbidities. Fire-setting treatments are addressed by overlapping disciplines: firefighters, the justice system, pediatric injury prevention specialists, child protection agencies, and mental health professionals. Treatment reflects education and public health techniques (Pinsonneault et al. 2002) aimed at safe behavior with regard to fire.

Distinguishing Pyromania From Other Fire-Setting Behaviors

Because of the heterogeneity of fire setting, which may be attributable to factors such as aggression, social skills deficits, vandalism, and antisocial behavior in addition to pyromania, a comprehensive initial interview is needed to determine the individual's dangerousness, suicidality, access to incendiaries, and motive, as well as environmental and social risks and triggers associated with recidivism. Assessments for children and adolescents include the Firesetting Incident Analysis—Parent Version (FIA-P) and Child Version (FIA-C), a Firesetting Risk Interview (FRI), and Children's Firesetting Inventory (CFI) (Kolko 1999). Pyromania can exacerbate mood, impulse-control, and substance abuse disorders (Grant and Kim 2007) and in some cases can precede them. The Minnesota Impulse Disorders Interview (MIDI) can accurately identify children and adolescents with impulse-control disorders (Grant and Kim 2007).

Neurobiological and Neurophysiological Bases of ICDs and Pyromania

ICDs may involve serotonergic, noradrenergic, dopaminergic, cholinergic, GABAergic, and glutamatergic dysfunction, as well as testosterone and endorphin dysfunction (Roncero et al. 2009). Impulsive fire setters may have low cerebrospinal fluid (CSF) concentrations of 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG), which are markers of central serotonin and norepinephrine, respectively (Virkkunen et al. 1989). A single-photon emission computed tomography (SPECT) imaging study in a patient, age 18 years, with pyromania demonstrated a left inferior frontal perfusion deficit that resolved after a course of cognitive-behavioral therapy (CBT) and topiramate treatment (Grant 2006).

Pharmacotherapy

Pharmacotherapeutic agents that have been used for treatment of ICDs include

typical and atypical antipsychotics (olanzapine), selective serotonin reuptake inhibitors (SSRIs) (escitalopram, sertraline, fluoxetine), β-blockers, naltrexone, stimulants, lithium, anticonvulsants (sodium valproate, topiramate, carbamazepine), antiandrogen agents, and clonazepam (Grant and Odlaug 2012; Hollander et al. 2008; Roncero et al. 2009). However, no double-blind randomized controlled trials and few case studies have been reported in the pyromania literature. Therefore, when selecting medications, clinicians must consider the neurobiological pathway and comorbidities they are treating on an individual basis (Table 44–1). Clinicians must advise patients about the off-label nature of pyromania pharmacotherapy. Some treatments useful in ICDs have been poorly tolerated in patients with pyromania (i.e., in those with comorbid bipolar disorder). For example, a boy age 9 years who was being treated for encopresis with escitalopram developed pyromania, which rescinded when the medication was withdrawn (Ceylan et al. 2011).

The case of the 18-year-old with pyromania (Grant 2006) whose symptoms resolved after treatment with topiramate and CBT (as described earlier in the section "Neurobiological and Neurophysiological Bases of ICDs and Pyromania") is but one example of anticonvulsants aiding patients with pyromania. One case study described a homeless man, age 20 years, with pyromania and cognitive impairment, anhedonia, a history of drug abuse, and depressive and paranoid symptoms. Magnetic resonance imaging indicated cerebral atrophy, and he had two tonic-clonic seizures. Treatment with sodium valproate and olanzapine ameliorated his pyromania (Parks et al. 2005). The anticonvulsant carbamazepine has also been successfully used to treat three boys with fire-setting behaviors and temporal lobe electroencephalographic abnormality (Milrod and Urion 1992). Antiandrogen medication has been suggested in clinical cases, as well (Bourget and Bradford 1987; Roncero et al. 2009).

Psychosocial Treatments

Psychosocial treatments for pyromania include short-term psychotherapy, day treatment programs, short-term inpatient hospitalization, and placement in residential treatment facilities. In one study, 90.5% of fire starters reported severe distress after committing the act of fire setting, and 38.1% had considered suicide as a viable means to controlling this behavior (Grant and Kim 2007). Therefore, suicide evaluation is essential in determining placement. Fire-setting behaviors may also require that mental health professionals collaborate with fire and police departments (Slavkin 2002). Challenges in treating these patients with pyromania include their refusal to take responsibility, denial, substance abuse, and poor insight (Mavromatis and Lion 1977).

Techniques to help extinguish fire-setting behaviors include CBT, behavioral therapy, graphing therapy, positive reinforcement, threats of punishment, operant structured fantasy, stimulus satiation, recognizing external stressors, fire safety education (FSE) utilizing fire safety professionals, and visits to burn units. Table 44–2 describes some studies using these techniques. An influential study (Kolko 2001) compared CBT with FSE and two firefighter home visits. Psychologist-administered CBT was used in an 8-week program addressing clinical factors seen with fire setting; techniques included graphing problem solving, assertion and

TABLE 44–1. Pharmacotherapy for pyromania

Pyromania (with associated features)	Pharmacological agent[a]	Source	Outcome (if known)
Psychosis	Atypical antipsychotic	Parks et al. 2005; author's expert opinion	Fire setting abated, cognitive function improved (with valproic acid adjunct)
Compulsive behavior	SSRIs[b] (escitalopram, sertraline, fluoxetine)	Grant and Kim 2007	
	Topiramate (corticomesolimbic dopamine function)	Grant 2006; Grant and Kim 2007	With cognitive-behavioral therapy, fire-setting urge abated
	Atypical antipsychotic	Parks et al. 2005	
Addiction	Naltrexone	Author's expert opinion	
Rage	Atypical antipsychotics	Author's expert opinion	
Trauma	Prazosin	Author's expert opinion	
	Naltrexone	Author's expert opinion	
	α Agonists	Author's expert opinion	
Developmental disability	α Agonists	Author's expert opinion	
Sexual disorder	Gonadotropin-releasing agents (leuprolide)	Author's expert opinion	
Bipolar disorder	Mood stabilizers (lithium)	Grant and Kim 2007	

TABLE 44–1. Pharmacotherapy for pyromania *(continued)*

Pyromania (with associated features)	Pharmacological agent[a]	Source	Outcome (if known)
Attention-deficit/hyperactivity disorder	Stimulants	Author's expert opinion	
Alcoholism (Type I—low 5-HT/5-HIAA alcoholics with fire setting and antisocial personality disorder)	SSRIs,[b] naltrexone	Author's expert opinion	
Antisocial personality disorder	SSRIs,[b] atypical antipsychotics, lithium, valproate	Author's expert opinion	
Depression or anxiety	SSRIs[b]	Grant and Kim 2007	

Note: 5-HT=serotonin; 5-HIAA=5-hydroxyindoleacetic acid; SSRI=selective serotonin reuptake inhibitor.
[a]Fluoxetine, valproic acid, olanzapine, escitalopram, citalopram, and clonazepam were found not to be effective in other case studies (Grant and Odlaug 2012).
[b]*Caution:* A case of pyromania associated with escitalopram use in a child has been reported.

TABLE 44–2. Psychosocial treatments for pyromania

Psychosocial intervention	Source	Result
Cognitive-behavioral therapy		
Eight 1-hour weekly visits • Graphing • Problem solving • Self-instruction • Assertiveness skills • Interpersonal conflict skills • Parent psychoeducation • Parent behavior management	Kolko 2001; Kolko and Sharf 2006	Significant reduction in fire setting, including at 1-year follow-up
3 weeks of daily 1-hour sessions • Imaginal exposure and response prevention • Cognitive restructuring of responding to urges • Relaxation training • (Concomitant with topiramate pharmacotherapy)	Grant and Kim 2007[a]	Symptom free, on medication for 20 months
Behavioral therapy relaxation training		
• Overt sensitization (visit to hospital burn unit) • Awareness training • Behavior substitution • Relaxation training • Response cost for fire setting	Koles and Jenson 1985[a]	Child fire setter, successful treatment at 1 year
Fire safety education		
• Firefighter educator • Parental involveme • Home-based contin	Kolko 2001; Kolko and Sharf 2006	Slightly less effective than cognitive-behavioral therapy but still effective based treatment

TABLE 44–2. Psychosocial treatments for pyromania *(continued)*

Psychosocial intervention	Source	Result
Graphing therapy		
• Correlate event, feeling, and behavior on a graph in front of patient and family • Help patient become aware of cause and effect between feeling and behavior • Sensitize child to feeling to recognize risk and then substitute appropriate behavior	Bumpass et al. 1983[b]	After average of 2.5 years, only about 7% recidivism
Community-based (multidisciplinary)		
Firefighters intervene with • Education • Behavioral modification • Graphing therapy • Negative consequences	Adler et al. 1994	Significant reduction in fire setting
Trauma Burn Outreach Prevention Program (TBOPP; ages 14–17 years) • 1 day • Impact of behavior and accountability focus • Parent attendance • Nurse educators, trauma surgeons, social workers, firemen, burn victims, former program graduates	Franklin et al. 2002	<1% recidivism in TBOPP group compared to 36% for no-therapy group
Interactive trauma burn, intensive care unit education with skin bank, morgue, injury prevention • Fire safety equipm		

interpersonal conflict resolution, parent education, behavior training, and an at-home module. Although all approaches were therapeutic, CBT had the greatest efficacy, followed by FSE, in reducing fire setting, fire interest, and playing with matches at 1 year. CBT had the greatest effect in diminishing fire-related behaviors and attraction (Kolko 2001; Lambie and Randell 2011). In some instances, FSE and 1-day intensive programs at burn units led to significant reductions in recidivism that rivaled CBT (for review, see Lambie and Randell 2011). Because fire-setting behavior is epidemiologically linked with psychopathology and substance use, and because youths who start fires earlier and with greater severity have histories of other behavior problems, it is imperative to catch the problem while the children are young, and to seek care of mental health and fire service professionals when fire-setting behaviors begin (MacKay et al. 2009).

Conclusion

Pyromania is an underrecognized disorder, and impulsive and nonmalicious fire-setting behavior is often overshadowed by the psychopathology more common in arson (with ill intent and secondary gain to the fire setting). Pyromania can lead to loss of property and loss of life—both by accidental fire and by suicide of the perpetrator. Few studies on pharmacotherapy and psychosocial therapy for pyromania exist. Case studies have reported excellent results with CBT, which is considered the first line of therapy. Combining CBT with anticonvulsant therapy (and possibly with atypical antipsychotics and antiandrogens) has been shown to be successful. The evidence base is sparse and in great need of expansion.

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CHAPTER 45

Kleptomania

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Kleptomania is characterized by repetitive stealing behavior that is precipitated by significant and uncontrollable urges to steal items not needed for one's personal use. Kleptomania is associated with significant psychosocial and legal consequences as well as elevated rates of suicide attempts (Odlaug et al. 2012). The DSM-5 criteria for kleptomania are shown in Box 45–1 (American Psychiatric Association 2013).

Despite being described in the medical literature since the nineteenth century (Esquirol 1838), kleptomania remains a poorly understood disorder with limited data regarding etiology, neurobiology, and treatment. Currently, no medication has received regulatory approval in any jurisdiction as a treatment for kleptomania, and there are no universally agreed upon psychosocial interventions for its treatment. In this chapter, we review the clinical aspects of kleptomania and the available research on the pharmacological and psychosocial treatments of kleptomania.

Box 45–1. DSM-5 Diagnostic Criteria for Kleptomania

312.32 (F63.2)

A. Recurrent failure to resist impulses to steal objects that are not needed for personal use or for their monetary value.
B. Increasing sense of tension immediately before committing the theft.
C. Pleasure, gratification, or relief at the time of committing the theft.
D. The stealing is not committed to express anger or vengeance and is not in response to a delusion or a hallucination.
E. The stealing is not better explained by conduct disorder, a manic episode, or antisocial personality disorder.

Clinical Characteristics

Onset of kleptomania is typically in early adulthood but has been reported in individuals as young as 4 years and as old as 77 years. The course of the illness is generally chronic with waxing and waning of symptoms. Women appear twice as likely as men to have kleptomania. Individuals with kleptomania frequently hoard, discard, or return stolen items. Of those who are married, less than half disclose their behavior to their spouses (Grant and Kim 2002b).

Most individuals with kleptomania try unsuccessfully to stop stealing. The inability to stop the behavior often leads to feelings of shame and guilt, and the majority of individuals with kleptomania have been apprehended at some time because of their stealing behavior. Examination of treatment-seeking samples demonstrates that kleptomania is highly comorbid with other psychiatric conditions. Evidence suggests that individuals with kleptomania have high rates of depression, anxiety, and substance use disorders. Suicidal ideation and attempts are extremely common and should be addressed at each visit when treating kleptomania (Odlaug et al. 2012).

The behaviors that characterize kleptomania (e.g., urges to steal, inability to stop) are impulsive in that they are often poorly thought out, risky, and result in deleterious long-term outcomes. Psychological testing has demonstrated that compared with control subjects, persons with kleptomania have greater cognitive impulsivity, larger deficits in inhibition, and greater sensation seeking (Baylé et al. 2003). One neuroimaging study comparing individuals with kleptomania with healthy control subjects found decreased white matter microstructural integrity in inferior frontal brain regions consistent with difficulties in impulse control (Grant et al. 2006).

Pharmacological Treatments

It is unknown how many individuals with kleptomania seek formal treatment, and scant treatment data exist for kleptomania. The available data appear to be confined to one double-blind study, two open-label studies, and case reports. Although no medications have been approved by regulatory boards for the treatment of kleptomania, pharmacotherapy has shown some early promise in treating this disorder.

Opioid Antagonists

Because individuals with kleptomania usually report uncontrollable urges to steal and excitement or a "rush" when stealing, a reward-triggered release of dopamine has been hypothesized as underlying these symptoms. Alterations in dopaminergic pathways may produce the feelings of pleasure often associated with kleptomania. As a result, opioid antagonists such as naltrexone, which are thought to decrease dopamine neurotransmission in the nucleus accumbens and the corresponding linked motivational neurocircuitry, have been proposed as beneficial agents in dampening the excitement and urges of kleptomania. The benefit of naltrexone, the most widely studied pharmacotherapy in treating this disorder, was first confirmed in case reports of use of naltrexone 150 mg/day in an adolescent with co-occurring kleptomania and compulsive sexual behavior (Grant and Kim 2001) and an adolescent with kleptomania (Grant and Kim 2002a).

The first open-label study for kleptomania also examined naltrexone. Ten sub-

jects with kleptomania were treated over 12 weeks with naltrexone, at escalating dosages (titrated from 50 to 100 to 150 to 200 mg/day over the course of treatment) (Grant and Kim 2002c). A mean dosage of 145 mg/day resulted in a significant decline in the intensity of urges to steal, stealing thoughts, and stealing behavior in 9 of the 10 subjects. A naturalistic study of naltrexone produced similar results (Grant 2005). Seventeen subjects were followed over a 3-year period while being treated with naltrexone (mean dosage=135.3 mg/day). Forty-one percent of the subjects reported complete abstinence from stealing, and 76% reported significant reductions in their urges to steal.

In the only placebo-controlled, double-blind study of kleptomania, 25 subjects were randomly assigned in a 1:1 fashion to receive either naltrexone or placebo for 8 weeks (Grant et al. 2009). By study endpoint, symptom remission was reported by 66.7% of those assigned to naltrexone compared with 7.7% of those given placebo ($P<0.001$). The mean effective dose of naltrexone was 116.7 mg/day. Although the double-blind study of naltrexone did not report any elevations of liver enzymes, opioid antagonists, particularly at doses higher than 50 mg/day, have been associated with hepatotoxicity. Based on this literature, naltrexone may be beneficial for kleptomania when kleptomania presents either by itself or in combination with a substance use disorder.

Antidepressants

Because low levels of the serotonin metabolite 5-hydroxyindoleacetic acid and blunted serotonergic response within the ventromedial prefrontal cortex have been associated with impulsive behaviors, serotonergic antidepressants have also been examined in the treatment of kleptomania (Lepkifker et al. 1999). One study examined the platelet serotonin (5-HT) transporter in 20 patients with kleptomania. The amount of the platelet 5-HT transporter, evaluated by means of binding of ^{3}H-paroxetine, was found to be lower in subjects with kleptomania than in a sample of control subjects, suggesting serotonergic dysfunction (Marazziti et al. 2000).

The only controlled study of an antidepressant for treatment of kleptomania began with a 7-week open-label trial of escitalopram, followed by randomization of the responders to either escitalopram continuation or placebo for an additional 16 weeks. Following randomization, 43% of those assigned to receive escitalopram relapsed, compared with 50% of those receiving placebo, thereby failing to demonstrate a drug effect (Koran et al. 2007).

Although there is no clear indication for the use of antidepressants in kleptomania, the fact that depression is commonly comorbid with kleptomania, and that suicide attempts are fairly common in individuals with kleptomania, suggests a potential important role for antidepressants in treating this disorder.

Other Agents

The anticonvulsant topiramate as monotherapy or as part of a combination therapy for kleptomania has also demonstrated positive symptom relief in a small case series. Topiramate 150 mg/day was reported as a successful treatment in an 18-year-old male with kleptomania, whereas the combination of topiramate 100 mg/day and paroxetine 60 mg/day was successful in a 32-year-old female with co-occurring kleptomania and obsessive-compulsive disorder. Finally, citalopram 30 mg/day plus topiramate 100 mg/day resulted in full remission of

kleptomania symptoms after 2 months of treatment in a 28-year-old female with kleptomania and panic disorder (Dannon 2003).

Case reports have illustrated the benefit of other monotherapies or combination pharmacotherapy for the treatment of kleptomania. Several medications, including paroxetine, fluoxetine, fluvoxamine, topiramate, valproic acid, and tolcapone, have shown benefit as monotherapy in kleptomania (Chong and Low 1996; Dannon 2003; Grant 2011; Kmetz et al. 1997; Kraus 1999). Also, the following combination medications have been reported as successful in treating kleptomania: paroxetine plus valproic acid plus naltrexone; topiramate plus paroxetine; naltrexone plus venlafaxine; lithium plus fluoxetine; trazodone plus tranylcypromine; sertraline plus methylphenidate; and imipramine plus fluoxetine (Burstein 1992; McElroy et al. 1991).

Psychosocial Treatments

To date, no controlled clinical trials of any psychosocial intervention for kleptomania have been reported. Case studies, however, suggest that forms of cognitive-behavioral therapy (CBT) may be a potentially promising treatment for kleptomania. Behavioral models conceptualize kleptomania as a learned pattern of reinforcement within a functional framework. Persistence in stealing is viewed as stemming from a variable pattern of reinforcement with respect to antecedents (e.g., financial pressure, external cues, positive or negative emotions, interpersonal factors), behaviors (e.g., use of stealing as a means of coping with negative affect), and consequences (e.g., distress, relationship conflict, positive consequences such as excitement). Behavioral treatments focus on altering one or more components of this functional relationship, with the goal of modifying the learned patterns. Cognitive treatment models focus specifically on modifying the maladaptive and distorted cognitions associated with stealing (e.g., the belief that acquiring something will address internal or interpersonal distress).

In a recent case study, Grant et al. (2012) reported on the successful use of six sessions of CBT using imaginal desensitization (i.e., recording the client's "typical" stealing episode) plus motivational interviewing in a 17-year-old male with kleptomania. The client was instructed to listen to the recording several times a day between sessions and to listen to it when an urge to steal presented itself. After successfully curbing his urges and stealing behaviors, the client completed maintenance sessions of therapy and reported no stealing at a 6-month post-therapy follow-up. This particular therapy has been shown to be helpful for other impulse-control disorders and is the first manualized therapy protocol for kleptomania (Grant et al. 2012).

Another case report describes a woman who was instructed to have increased nausea when tempted to steal with imagery of vomiting associated with actual stealing. Following four sessions over 8 weeks, the woman was able to go with only a single lapse in behavior over the next 19 months (Glover 1985). Similarly, aversive breath-holding in combination with diary keeping of urges to steal and six weekly sessions of therapy resulted in significantly reduced stealing frequency (Keutzer 1972).

A man was able to reduce the frequency of his shoplifting after undergoing seven sessions of covert sensitization combined with exposure and response

prevention over a 4-month period (Guidry 1975). Five weekly sessions of covert sensitization also were reported to help a young woman go 14 months with only a single lapse in behavior and with no reported urges to steal (Gauthier and Pellerin 1982). Another woman, age 77 years, responded well to both covert sensitization and a self-imposed ban on shopping (McNeilly and Burke 1998).

Case reports have also illustrated the benefit of combining medication with CBT. Successful examples of combined psychotherapy and pharmacology for the treatment of kleptomania include fluoxetine 40 mg/day combined with supportive psychotherapy; fluoxetine 40 mg/day combined with problem-oriented psychotherapy; fluoxetine 20 mg/day plus cognitive therapy; a combination of CBT, sertraline 50 mg/day, and a self-imposed shopping ban; and a combination of CBT and citalopram 40 mg/day (Aizer et al. 2004; Lepkifker et al. 1999; McNeilly and Burke 1998). More recently, case reports have demonstrated the effectiveness of topiramate 100 mg/day and CBT with imaginal desensitization in a 54-year-old female with comorbid kleptomania and attention-deficit/hyperactivity disorder (ADHD) (Talih 2011); dialectical behavioral therapy plus duloxetine in a 53-year-old male (Rudel et al. 2009); and methylphenidate (36 mg/day) and supportive therapy for an adolescent with kleptomania and ADHD (Hergüner and Tanidir 2011).

Conclusion

Kleptomania, a largely unrecognized disorder, presents as a chronic illness for many individuals and causes significant psychological, social, and legal repercussions. Because presentation specifically for kleptomania is quite rare, it is important that clinicians screen for the disorder and its comorbidities. Treatment recommendations are difficult to make given the extremely limited amount of information regarding pharmacotherapy and psychotherapy of kleptomania. Because the opiate antagonist naltrexone has demonstrated benefit in a placebo-controlled, double-blind study, it should be considered a first-line treatment. Psychotherapy, such as CBT, may be beneficial as well. There is a substantial need for systematic studies of the treatment of this disorder.

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Useful Web Sites

Addictive, Compulsive and Impulsive Disorders Research Program; University of Chicago. Homepage. Available at: http://aic.uchicago.edu. Accessed September 1, 2012.

National Association for Shoplifting Prevention. Homepage. Available at: http://www.shopliftingprevention.org/main.asp. Accessed September 1, 2012.

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PART X

Substance-Related and Addictive Disorders

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Substance use disorders are a significant public health problem that can lead to devastating consequences for the affected individuals, their families, and society. It is estimated that over 18% of Americans suffer from a substance use disorder at some point in their lifetime, with an economic cost of $560 billion, which is even more than the cost of dementia. Moreover, substance use disorders are overrepresented in individuals seeking medical and psychiatric treatment. Conservatively, at least 20% of medical patients and 30% of psychiatric patients have a concomitant substance use disorder.

Despite the fact that co-occurring substance use often precipitates or exacerbates the medical or psychiatric disorder, the substance use disorder frequently goes untreated. Although there has been a burgeoning growth in our understanding of the neurophysiology, genetic underpinnings, and chronic pathological changes associated with addiction, many clinicians are unaware of these dramatic advances. Further, despite the therapeutic discoveries that have been made in the past decade, some clinicians remain unaware of the numerous effective psychosocial and pharmacological treatments that are available for their patients. For example, many programs or clinicians refuse to use medications such as buprenorphine because of their 12-step orientation.

However, there has been some noticeable change. With increased attention paid to substance abuse training in medical school and residency, young physicians are more aware of how to recognize and refer patients to substance abuse treatment. Additionally, with the growing problem of prescription opiate abuse, physicians in practice are increasingly interested in how to identify problematic use and want training in how to better help these patients.

Importantly, the newly published fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) eliminates the disorder categories of abuse and dependence, with disorders classified as "substance-related and addictive disorders." By removing the category of dependence, the DSM-5 authors hope to distinguish between, on the one hand, the common responses of tolerance and withdrawal that some individuals experience when they are prescribed medications that affect the central nervous system and, on the other, compulsive drug-seeking behaviors associated with addiction. Most of the abuse and dependence symptoms in DSM-IV have been subsumed into DSM-5 substance use disorder symptoms.

The DSM-5 criteria that define a substance use disorder are listed in Box 1. The symptom of "drug craving" has been added to the substance use disorder criteria, whereas the symptom "repeated drug-related legal problems," formally part of the DSM-IV abuse criteria, has been removed. Notably, unlike DSM-IV, DSM-5 recognizes that prolonged, heavy use of cannabis may result in a clear-cut withdrawal syndrome characterized by a constellation of psychiatric and physical symptoms. DSM-5 has a new category, "Non-Substance-Related Disorders," which currently comprises only one disorder, gambling disorder. In DSM-IV gambling disorder was considered an impulse-control disorder not elsewhere classified. However, because there is substantive evidence that pathological gambling and substance use disorders are very similar in how they impact the brain reward system and are both associated with poor impulse control, pathological gambling is now considered an addiction in DSM-5. The diagnostic categories associated with each group of substances are shown in Table 1.

Box 1. Criterion A for Substance Use Disorder

A. A problematic pattern of use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
   1. The substance is often taken in larger amounts or over a longer period than was intended.
   2. There is a persistent desire or unsuccessful efforts to cut down or control use.
   3. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
   4. Craving, or a strong desire or urge to use the substance.
   5. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home.
   6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
   7. Important social, occupational, or recreational activities are given up or reduced because of substance use.
   8. Recurrent substance use in situations in which it is physically hazardous.
   9. Continued substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of the substance.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic substance withdrawal syndrome.
    b. The substance is taken to relieve or avoid withdrawal symptoms.

Because the addiction field is vast, it is beyond the scope of the chapters in this part to provide a sweeping overview. Instead, each of the chapters focuses on treatments for the various substances or behaviors that may lead to addiction and current psychotherapeutic and pharmacological approaches provided in real-world settings. In Chapter 46, "Alcohol-Related Disorders," John Mariani reviews the current state of the art regarding the pharmacological treatments for alcohol use disorder (alcohol dependence), ranging from detoxification to relapse prevention. Disulfiram was the first treatment approved by the Food and Drug Administration for alcohol dependence, in 1951. Oral naltrexone and acamprosate were subsequently approved, with the most recently FDA-approved treatment for alcohol dependence being depot naltrexone administered as an intramuscular injection. Experimental work in this area continues to seek out new medications to treat alcohol dependence to bolster psychotherapeutic interventions.

While misuse of benzodiazepines has been stable during the past decade, problematic use remains a chronic problem, particularly when combined with other substances. Unfortunately, there remain few studies that have focused on how to best treat this recalcitrant condition. In Chapter 47, "Sedative-, Hypnotic-, or Anxiolytic-Related Disorders," Domenic Ciraulo reviews the current treatments utilized in clinical practice.

Rates of heroin addiction have remained stable, with about 800,000 to 1 million individuals addicted to heroin. Prescription opiate misuse and addiction have become increasingly problematic in the past few years, particularly in rural settings and among adolescents, with numbers two to three times that of heroin. Although maintenance treatments are clearly the most effective approach to prevent relapse, a substantial number of opioid-dependent individuals only want detoxification. In Chapter 48, "Opioid-Related Disorders: Opioid Detoxification," Meredith Kelly and Herbert Kleber discuss the pros and cons of the commonly used withdrawal methods and some of the more recent strategies that are being tested.

Unlike with other drugs of abuse, the most effective pharmacological treatment approaches for substance use disorders are those for opiate dependence. In Chapter 49, "Opioid-Related Disorders: Antagonist Treatment," Kyle Kampman and Charles O'Brien review the utility of antagonists treatment for opiate dependence as well as the already mentioned development, intramuscular depot naltrexone. In the past, oral naltrexone's effectiveness was limited by poor adherence, except in highly motivated patients. The use of the depot formulation may circumvent the low retention rates but a formidable problem remains—how to increase its adoption in clinic and office settings.

TABLE 1. Diagnoses associated with substance class

	Psychotic disorders	Bipolar disorders	Depressive disorders	Anxiety disorders	Obsessive-compulsive and related disorders	Sleep disorders	Sexual dysfunctions	Delirium	Neurocognitive disorders	Substance use disorders	Substance intoxication	Substance withdrawal
Alcohol	I/W	I/W	I/W	I/W		I/W	I/W	I/W	I/W/P	X	X	X
Caffeine				I		I/W					X	X
Cannabis	I			I		I/W		I		X	X	X
Hallucinogens												
Phencyclidine	I	I	I	I				I		X	X	
Other hallucinogens	I*	I	I	I				I		X	X	
Inhalants	I		I	I				I	I/P	X	X	
Opioids			I/W	W		I/W	I/W	I/W		X	X	X
Sedatives, hypnotics, or anxiolytics	I/W	I/W	I/W	W		I/W	I/W	I/W	I/W/P	X	X	X
Stimulants**	I	I/W	I/W	I/W	I/W	I/W	I	I		X	X	X
Tobacco						W				X		X
Other (or unknown)	I/W	I/W	I/W	I/W	I/W	I/W	I/W	I/W	I/W/P	X	X	X

Note. X = The category is recognized in DSM-5.
I = The specifier "with onset during intoxication" may be noted for the category.
W = The specifier "with onset during withdrawal" may be noted for the category.
I/W = Either "with onset during intoxication" or "with onset during withdrawal" may be noted for the category.
P = The disorder is persi
*Also hallucinogen pers

The congressional ratification of the Drug Addiction Treatment Act (DATA) in 2000, allowing the administration of buprenorphine in office-based settings, has greatly expanded opiate maintenance treatment in the community. The most commonly used formulation, suboxone (buprenorphine and naloxone), has been well accepted in the treatment community. These developments have dramatically increased treatment options for patients in dire need of treatment. However, methadone maintenance is a critical treatment option for more than 200,000 patients in the United States. Richard Schottenfeld and Carla Marienfeld discuss, in Chapter 50, "Opioid-Related Disorders: Agonist Maintenance Treatment," how to best use methadone and buprenorphine in clinic and office settings.

Hallucinogens continue to be used at a steady level, particularly in adolescents and young adults. In Chapter 51, "Hallucinogen-Related Disorders," Robert Pechnick, Kathryn Cunningham, and Itai Danovitch discuss some of the interventions used to counter the toxicity associated with the use of lysergic acid diethylamide, dimethyltryptamine, and dimethoxymethylamphetamine.

By far, the most commonly abuse illicit drug is cannabis. After alcohol, it is the most commonly reported drug resulting in emergency room admission. Although cannabis withdrawal had been observed since the late 1970s, it was not until the adoption of DSM-5 that it was formally recognized as a clear-cut reproducible constellation of symptoms contributing to the diagnostic criteria. Whereas it was commonly believed that chronic marijuana use is benign and easy to stop, the potential psychiatric consequences and increased potency of marijuana over the past decade have proven that this is not the case in a substantial minority of heavy users. Taken, together, these factors may have contributed to the higher observed rates of problematic use in the past few years. In Chapter 52, "Cannabis-Related Disorders," Kevin Gray and Frances Levin review the currently available and empirically tested psychotherapeutic options as well as promising pharmacological treatments that might be effective, although not FDA approved, for cannabis use disorder.

In Chapter 53, "Club Drug Addiction," Michael Weaver, Christina Delos Reyes, and Sidney Schnoll address the “club drugs” MDMA (methylenedioxymethamphetamine), ketamine, phencyclidine, and gamma-hydroxybutyrate, which remain popular in urban areas in the United States. Often, abuse of club drugs is recognized when individuals present to emergency settings as a result of the toxic consequences of these drugs.

Cocaine use has shown a sharp decline since the major epidemic in the 1980s. There has been a reduction in cocaine dependence as well, though certainly not as steep as for cocaine use. Despite these welcome improvements, there remain at least 1 million Americans dependent on cocaine, with the dependence often refractory to treatment. To date, there are no FDA-approved treatments for cocaine dependence. However, there is an extensive pharmacological treatment literature testing a wide range of agents. In Chapter 54, "Stimulant-Related Disorders," Mehmet Sofuoglu and Ariadna Forray review the current pharmacological agents that show promise, as well as innovative approaches, such as “cocaine vaccines.”

Robert Anthenelli reviews, in Chapter 55, "Nicotine-Related Disorders," the growing armamentarium to alleviate nicotine withdrawal and treat tobacco use disorder. Although nicotine dependence continues to decline in the United

States, there remains 57 million Americans who are current cigarette smokers. Often, comorbid psychiatric disorders are present, making smoking cessation more difficult. While nicotine replacement therapies are most commonly used, other FDA-approved agents are available, such as bupropion and varenicline. Recently, there has been increased recognition that combined pharmacotherapies might work best in promoting abstinence. Practitioners often ignore their patients' smoking out of a belief that other problems are of more pressing concern. Unfortunately, this is particularly true of psychiatrists. Successful interventions for nicotine addiction, however, do not need to be time-consuming and can be of great help to the person's overall health. Dr. Anthenelli provides the tools for clinicians to be of such assistance.

While the development of medications for the treatment of substance abuse is an intense area of research, the mainstay of treatment is psychotherapeutic approaches. In Chapter 56, "Individual Therapy for Substance Use Disorders," George Woody discusses the critical role that individual psychotherapy plays in effective substance abuse treatment. Kenneth Carpenter, Daniel Moran and Edward Nunes summarize, in Chapter 57, "Cognitive, Behavioral, and Motivational Therapies for Substance Use Disorders," cognitive, behavioral, and motivational therapies. These approaches have been increasingly used, but much as with medications, there are practical barriers that often limit adoption in community settings. To increase adoption in community settings, novel computerized interventions have been developed. These approaches are summarized as well. In Chapter 58, "Group Therapy for Substance Use Disorders" Arnold Washton succinctly reviews the advantages and disadvantages of group therapy, the most commonly used group therapy approaches, and important considerations in setting up substance abuse treatment groups. In Chapter 59, "Family Therapy in Substance Abuse Treatment," Peter Steinglass reviews family therapies and their role as a core component of treatment. Notably, one particular treatment, CRAFT (Community Reinforcement and Family Training), has been shown to be effective in teaching spouses or concerned significant others in the family to avoid confrontation around substance abuse and instead focus on positive reinforcement and relies on techniques similar to those utilized by other successful treatment engagement programs. Finally, in Chapter 60, "Network Therapy in Substance Abuse Treatment," Marc Galanter uses the insights of psychiatry along with family and peer support techniques in a combination called *network therapy.*

Two new additions to this section are a chapter on pain and addiction and another on gambling. In Chapter 61, "Pain and Addiction," Maria Sullivan offers strategies for distinguishing opiate use for chronic noncancer pain and opiate addiction as well as clinical approaches when pain patients are misusing/abusing their medications. Finally, in Chapter 62, "Gambling Disorder," Carlos Blanco and Silvia Bernardi discuss the current available treatments for gambling disorder (pathological gambling). While cognitive-behavioral therapy approaches have the greatest evidence for efficacy, other approaches, including pharmacological ones, show promise.

In sum, clinicians will find that the chapters provided offer a concise summary of valuable state-of-the-art treatment strategies.

CHAPTER 46

Alcohol-Related Disorders

John J. Mariani, M.D.

Alcohol use disorder is among the most common health problems that psychiatrists encounter in general practice, with past yearly prevalence rates of approximately 8.5% (Stinson et al. 2005), and is a leading cause of preventable death (Mokdad et al. 2004). Familiarity with diagnosing and treating common alcohol-related disorders is a core competency of general psychiatrists. Although specialty settings are appropriate for more severe and complicated cases, most patients with alcohol use disorder can be managed as outpatients, and psychiatrists can and should play a central role in their treatment. Because alcohol use disorder can present as a component of a myriad of chief complaints in a wide variety of health care delivery settings, behavioral health clinicians should be competent in the basic approach to treating this disorder.

Diagnostic Issues

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) eliminates the substance abuse and dependence diagnoses and criteria sets and subsumes them into a new category, *substance use disorders* (American Psychiatric Association 2013). Severity specifiers (two or three criteria for *mild*, four or five criteria for *moderate*, and six or more criteria for *severe*) replace the "abuse" and "dependence" diagnoses. The DSM-5 substance use disorder criteria set is essentially a combination of the abuse and dependence criteria sets. Because the DSM-IV substance dependence diagnosis (American Psychiatric Association 1994) had the potential to unintentionally communicate physiological dependence, this change in nomenclature will likely result in clearer clinical communication, particularly with nonpsychiatric medical colleagues.

Treatment Engagement

Individuals with alcohol use disorder are often not willing to engage in a treatment process to address their alcohol use, or they present for treatment with other primary complaints such as medical illness or depression. The foundation

of any successful treatment for alcohol use disorder is to help the patient address alcohol use as a treatment goal. The most effective approach for promoting treatment engagement is the use of the clinical framework *motivational interviewing* (MI) developed by Miller and colleagues (Miller and Rose 2009). MI aims to use empathy, reflective listening, and an interpersonal framework to elicit patient "change talk." This approach is in contrast to more traditional confrontational approaches, such as employed in an "intervention," where the consequences of alcohol use are presented to the individual, often in a dramatic manner, in an effort to induce treatment-seeking behavior. Although patient-centered approaches to facilitate treatment engagement are in general preferred because of the higher likelihood of success, in situations where patient safety is at risk and the need for treatment is urgent, more confrontational and direct recommendations may be indicated.

Medically Supervised Treatment of Alcohol Withdrawal

For individuals with alcohol use disorder, neuroadaptation of the brain to the presence of alcohol can lead to the development of an alcohol withdrawal syndrome when drinking ceases. The alcohol withdrawal syndrome can range from mild symptoms of anxiety, irritability, and insomnia to a severe pathophysiological state characterized by autonomic nervous system hyperactivity with elevated pulse, blood pressure, and seizures. A primary consideration when developing a treatment plan for a patient with alcohol use disorder is the presence of, or risk of developing, alcohol withdrawal. The revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar; Sullivan et al. 1989) is the standard scale for measuring alcohol withdrawal symptoms (Table 46–1).

The CIWA-Ar prompts the clinician to rate 10 symptoms on a scale of 0 to 7. A CIWA-Ar total score of more than 15 or a history of alcohol withdrawal seizures indicates that medication treatment for withdrawal should be instituted immediately. In cases where medication treatment is not indicated, alcohol withdrawal symptoms are expected to peak about 72 hours after the last use of alcohol. Cases of severe alcohol withdrawal leading to an alcohol withdrawal delirium (delirium tremens) require high-dose benzodiazepine treatment, typically in an intensive care setting.

The gold standard for pharmacological management of alcohol withdrawal remains benzodiazepines (Holbrook et al. 1999; Mayo-Smith 1997). In general, long-acting benzodiazepines such as chlordiazepoxide, clonazepam, diazepam, or oxazepam are preferred. However, because rapidly acting benzodiazepines such as diazepam, alprazolam, and lorazepam have greater misuse liability (Griffiths and Wolf 1990), these agents should be avoided for withdrawal treatment in the outpatient setting. Phenobarbital was historically a standard treatment for alcohol withdrawal, but there is no controlled trial evidence supporting the use of barbiturates, and as a class, barbiturates have an unfavorable safety profile when compared with benzodiazepines, particularly the risk of respiratory depression when combined with alcohol.

There has been great interest in developing nonbenzodiazepine treatment alternatives for alcohol withdrawal, because in the outpatient setting benzodiazepines present the risk of misuse and

TABLE 46–1. Revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)

1. Nausea and vomiting: Ask *"Do you feel sick to your stomach? Have you vomited?"* Observation.
2. Tremor: Assess patient with arms extended and fingers spread apart. Observation.
3. Paroxysmal sweats: Observation.
4. Anxiety: Ask *"Do you feel nervous?"* Observation.
5. Agitation: Observation.
6. Tactile disturbances: Ask *"Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?"* Observation.
7. Auditory disturbances: Ask *"Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?"* Observation.
8. Visual disturbances: Ask *"Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?"* Observation.
9. Headache, fullness in head: Ask *"Does your head feel different? Does it feel like there is a band around your head?"* Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
10. Orientation and clouding of sensorium: Ask *"What day is this? Where are you? Who am I?"*

Source. Sullivan et al. 1989.

have additive sedative and respiratory depressant effects when combined with alcohol. The evaluation of anticonvulsant drugs has yielded some promising results (Ait-Daoud et al. 2006; Leggio et al. 2008), particularly for carbamazepine (Björkqvist et al. 1976; Malcolm et al. 2002) and gabapentin (Mariani et al. 2006; Myrick et al. 2009). These agents offer an advantage over benzodiazepines for mild to moderate cases of alcohol withdrawal treated in the outpatient setting. However, for the treatment of moderate to severe alcohol withdrawal in the inpatient setting, anticonvulsant medications have not been proven to prevent the development of withdrawal delirium, and benzodiazepines remain the treatment of choice.

Antidipsotropic Medications

Several medications have been shown to be effective at preventing relapse in abstinent patients or promoting reductions in alcohol use or achievement of abstinence in those who are drinking. These antidipsotropic medications have different pharmacological and clinical characteristics, which need to be taken into consideration when developing a treatment plan for an individual with alcohol use disorder. The available medications used to treat alcohol use disorder have potential benefit at a particular clinical stage (Table 46–2).

TABLE 46–2. Antidipsotropic medications

Medication	Clinical activity	Ideal patient characteristics	Precautions, adverse effects, and limitations
Acamprosate	Reduction of craving leading to relapse prevention	Already abstinent with intention to remain abstinent	Dosing is three times daily; diarrhea and nausea are common. Magnitude of clinical effect is modest.
Disulfiram	Inhibition of aldehyde dehydrogenase, which leads to buildup of acetaldehyde when alcohol is ingested; deterrent to alcohol consumption	Already abstinent with intention to remain abstinent; mechanism (either family or treatment providers) to supervise administration	Headache, skin rash, and drowsiness are common even if alcohol is not consumed. Less common but severe adverse reactions include hepatitis and peripheral neuropathy.
Naltrexone	Inhibition of rewarding effects of alcohol or alcohol-related cues, leading to reduction in alcohol consumption or reduced rates of relapse	Abstinent or actively drinking; a long-acting intramuscular formulation available to ensure compliance	Nausea and abdominal pain are common. Cannot combine with opioid pain medications. Magnitude of the clinical effect is modest.
Topiramate	Inhibition of rewarding effects of alcohol or alcohol-related cues, leading to reduction in alcohol consumption or reduced rates of relapse	Abstinent or actively drinking	Paresthesia is very common, and difficulty with concentration is often intolerable. Long titration phase to reach active dose. Magnitude of the clinical effect is modest.

Naltrexone, a μ opioid receptor antagonist, is the most widely studied medication for the treatment of alcohol use disorder and is approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcohol use disorder. Meta-analytic studies have found that naltrexone treatment is effective at reducing alcohol consumption in individuals with alcohol use disorder (Bouza et al. 2004; Kranzler and Van Kirk 2001; Rösner et al. 2010), as well as reducing the risk of relapse (Streeton and Whelan 2001). The available evidence supports the conclusion that the main clinical effect of naltrexone is the reduction of heavy drinking (Pettinati et al. 2006). Naltrexone is typically prescribed in an oral form at a dosage of 50 mg/day, although a long-acting injectable formulation has also been shown to be effective (Garbutt et al. 2005; Kranzler et al. 2004) and may be a superior option for those patients for whom compliance is a concern. The addition of gabapentin, a sedating and anxiolytic anticonvulsant agent, to naltrexone can improve drinking outcomes (Anton et al. 2011). Naltrexone is a good pharmacotherapy choice for an individual with alcohol use disorder who does not have a goal of abstinence and is actively drinking at the time of initiation of therapy.

Acamprosate, an *N*-methyl-D-aspartate receptor modulator, has been widely studied in Europe and the United States and is FDA approved for the treatment of alcohol use disorder. Meta-analytic studies demonstrate a benefit in enhancing abstinence rates (Kranzler and Van Kirk 2001; Mann et al. 2004), although multisite trials conducted in the United States in which patients were not required to achieve pretrial abstinence have not shown benefit (Anton et al. 2006; Mason et al. 2006). These results suggest that patients must achieve pretreatment abstinence in order to experience benefit from acamprosate. The Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) study, a multisite trial comparing naltrexone and acamprosate and a combination of both with placebo, found no benefit to treatment with both medications simultaneously (Anton et al. 2006). Acamprosate is a good medication choice for an individual with alcohol use disorder who has a goal of abstinence for alcohol and who will have a period of pretreatment abstinence, ideally in a controlled therapeutic environment.

Disulfiram is the oldest available FDA-approved medication for the treatment of alcohol use disorder. Disulfiram inhibits the metabolism of alcohol, resulting in unpleasant symptoms from the disulfiram-alcohol reaction, thereby acting as a deterrent to alcohol use when ingested. The main limitation of disulfiram is that poor compliance with the medication can limit therapeutic benefit, so there is a recognized need for supervised administration to achieve maximal benefit. Meta-analytic review has found that supervised disulfiram treatment is associated with improved abstinence and less alcohol consumption (Jørgensen et al. 2011). Disulfiram is a good medication choice for an individual with alcohol dependence who has a goal of complete abstinence and who either has a family member willing to supervise administration or is attending a treatment program that can supervise administration.

The anticonvulsant agent topiramate has been shown to be effective in reducing heavy drinking in a manner similar to that of naltrexone (Johnson et al. 2003, 2007). Although the clinical benefit of reducing heavy drinking as opposed to the achievement of abstinence may be questioned, the reduction in drinking has been shown to improve physical health and quality of life (Johnson et al. 2004, 2008). A potential advantage of topira-

mate is the ability to achieve a clinical benefit without first achieving pretreatment abstinence. Topiramate's utility is similar to naltrexone; it is a good medication choice for an individual who has the goal of moderation as opposed to abstinence and who is actively drinking at the time of treatment initiation.

Behavioral Treatment

When considering behavioral treatment of alcohol use disorder, the clinician must address two questions: 1) what type of behavioral treatment would be best for this patient, and 2) where should this treatment be delivered? Historically, 12-step-oriented treatment (e.g., Alcoholics Anonymous) was the standard. Although many treatment programs continue to deliver treatment based on Twelve Step program philosophy, other evidence-based treatments have been developed and are increasingly available. The strongest evidence of efficacy has been found for brief interventions, the community reinforcement approach, behavioral contracting, behavioral marital therapy, and case management (Miller and Wilbourne 2002). The effect sizes for cognitive-behavioral treatments for substance use disorders are comparable to those of interventions for other psychiatric disorders, with the greatest effect sizes obtained for contingency management approaches (Dutra et al. 2008). However, the contingency management model, in which the patient is provided either money or other valuable rewards for desired behavior (e.g., negative urine drug tests or treatment attendance), has been difficult to adapt to community treatment settings, and its availability remains limited. In addition, the effects tend to dissipate once the rewards end unless treatment is combined with other behavioral interventions.

Twelve-step facilitation (TSF) therapy is a professionally delivered intervention that promotes the patient's involvement in 12-step group participation. However, it is important to note that most community treatment programs that are "12-step oriented" are not delivering an empirically tested treatment. The multicenter Project MATCH (Matching Alcoholism Treatments to Client Heterogeneity) study found that TSF was as effective as cognitive-behavioral therapy (CBT) (Project MATCH Research Group 1998). However, arguably, TSF and CBT are probably each better suited to a specific profile of patient. TSF, in line with 12-step principles, has abstinence as the only acceptable treatment goal, and CBT has the flexibility to permit more limited goal setting within the structure of the treatment. For example, for an individual with a clear treatment goal of abstinence and a history of past 12-step group participation leading to abstinence from alcohol, a TSF or other 12-step-oriented treatment is likely to be helpful. For an individual with moderation of alcohol use as a goal, a combined MI and CBT approach would be a better match to the treatment goal than TSF. Although MI and CBT are patient-centered approaches that focus on addressing the patient's goals for treatment, it should be noted that abstinence is the most stable form of remission for individuals with an alcohol use disorder (Dawson et al. 2007).

An important development in the field of behavioral research on alcohol use disorder is the accumulating evidence that brief interventions for alcohol use disorders are effective (Vasilaki et al. 2006), particularly in acute hospital settings (McQueen et al. 2011). These interven-

tions involve a time-limited intervention focusing on changing behavior and range from providing psychoeducation about alcohol use problems to providing one to three sessions of MI or skills-based counseling. The advantage of these approaches is that they can be delivered in settings where patients with alcohol use disorder are identified, such as hospitals and other general medical settings.

Marital and family therapy can be critical in helping individuals with alcohol use disorder who are unwilling to seek treatment. Al-Anon, a 12-step group for family members, or facilitation and spouse coping skills training can help family member functioning, and the community reinforcement and family therapy approach promotes treatment entry of the identified patient (O'Farrell and Clements 2012). After the identified patient has entered treatment for alcohol use disorder, behavioral couples therapy can promote abstinence and improved relationship functioning.

Treatment Settings

Deciding on the appropriate setting for treatment is an essential aspect of treatment planning for a patient with alcohol use disorder. The first consideration is safety; for patients in severe alcohol withdrawal or who have unstable co-occurring medical or psychiatric conditions, an inpatient setting is indicated. For the majority of patients who do not have acute safety or medical concerns, outpatient treatment is usually appropriate and well accepted. Typically, patients will seek the least restrictive treatment option available.

Outpatient treatment options for alcohol use disorder include a spectrum of options ranging from individual psychotherapy through intensive outpatient programs (IOPs), in which patients will attend group therapy treatment every day for most of the day. Outpatient groups, usually focused on development of relapse prevention skills, can be combined with individual treatment. Twelve-step groups are widely available and can serve as a useful adjunct to professionally delivered treatment. Deciding on what intensity of outpatient treatment to recommend depends on the clinical status of the patient and the patient's goals and motivation. For example, a patient reluctant to set abstinence as a goal and in general resistant to engaging in treatment at an intense level may be best served by individual MI treatment. A patient with a treatment goal of abstinence who has been unable to stop drinking on his or her own could be referred to an IOP for more intensive support. After a period of stabilization in an IOP, a combination of weekly individual and group cognitive-behavioral therapy for maintenance of relapse prevention skills might be indicated. As treatment progresses, resources can be modified as needed, adding or dropping therapeutic interventions or varying the intensity of treatment.

For patients with alcohol use disorder who require inpatient treatment, a specialized "detox" unit is often the point of entry into the system of care. These units have staff trained in the medical management of acute alcohol withdrawal and are usually located in general medical hospitals. After stabilization, patients can be transferred either to other inpatient care, such as a residential treatment center, or to an outpatient treatment program.

Residential programs specialized for the treatment of substance use disorders provide a substance-free environment and are indicated in cases where safety concerns preclude outpatient treatment

or when adequate progress has not been made in outpatient treatment. The advantage that residential treatment programs ("inpatient rehab") provide over the outpatient setting is the separation of the patient from his or her home environment and removal of the availability of alcohol. Disadvantages of residential treatment are disruptions to the patient's occupational and family functioning and higher cost than outpatient treatment. After discharge from residential treatment, continuing treatment ("aftercare") is necessary to help maintain abstinence. Often, after discharge from a residential treatment program, an IOP treatment is indicated because return to the home environment, with the availability of alcohol and associated cues, is a challenging transition period. Residential treatment should be seen as a component of an ongoing system of care, not an endpoint where a patient will return to the community "cured."

Antidipsotropic medication treatment should be considered as an adjunct to any of the above-described behavioral treatment setting options. The choice of medication should be matched to the treatment goals. For example, a patient with clear abstinence goals and a spouse involved in treatment would make a good candidate for supervised disulfiram treatment. A patient with moderation use goals would be better served by naltrexone or topiramate treatment. Diagnosis and management of co-occurring psychiatric conditions at all stages of treatment will optimize chances of a good therapeutic outcome. For patients with co-occurring severe mental illnesses and alcohol use disorder, treatment often needs to be provided in a specialized setting, with staff trained to manage both severe psychiatric illness and substance use disorders, to achieve the best possible outcome (Horsfall et al. 2009).

Conclusion

Alcohol use disorder is a common and burdensome health problem encountered in a variety of psychiatric and general medical health care settings. Diagnostic and safety assessments are the first steps in developing a treatment plan. A wide variety of behavioral and medication treatment options are available for the treatment of alcohol use disorder, and patient characteristics and goals should be matched to the treatment and treatment setting. Involvement of family and other significant others can promote achievement of treatment goals. The intensity and elements of treatment can be adjusted over time in response to the patient's clinical status.

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CHAPTER 47

Sedative-, Hypnotic-, or Anxiolytic-Related Disorders

Domenic A. Ciraulo, M.D.

Drugs Classified as Sedative-Hypnotics

A chemically diverse group of agents are classified as *sedative-hypnotics,* linked by the ability to induce calm, sedation, sleep, respiratory depression, and coma. (For a detailed review of the pharmacology, see Ciraulo 2014.) Many of the drugs share the property of exerting their pharmacological effects at the gamma-aminobutyric acid (GABA) receptor, but recent research has revealed that these actions at the receptor differ among the agents. Furthermore, emphasis on GABA proved overly simplistic, ignoring both the variety of receptor subtypes and other neurotransmitter systems that have a profound influence on clinical activity and addiction potential. Therefore, in this chapter I address each class of agents individually, emphasizing shared properties and unique characteristics that often explain clinical differences in action. The discussion that follows is limited to agents that act at the $GABA_A$ receptor, including benzodiazepines, the Z drug hypnotics, and barbiturates.

Historical Background

Ethanol analogues were among the first medically used sedative-hypnotics and included paraldehyde, ethchlorvynol, and chloral hydrate. Also among the earlier agents were the piperidinedione derivatives, such as methyprylon and glutethimide. These drugs had high abuse potential, rapid tolerance, and low therapeutic indices, leading to lethal overdoses at dosages only somewhat higher than those in the therapeutic range, especially when combined with ethanol. Barbiturates have been prescribed since the 1900s, but they, too, were associated with fatal overdoses and even when used in prescribed doses were associated with drug interactions, inducing drug metabolism and producing additive central nervous system (CNS) depression with

alcohol. Meprobamate was introduced in 1955 and was quickly adopted as an effective antianxiety agent. With continued clinical use, the potential for abuse, toxicity, and tolerance became apparent.

After the first benzodiazepine, chlordiazepoxide, was introduced, these agents gradually replaced older agents for the treatment of anxiety and insomnia. The benzodiazepines were an important advance in medication development. They were far safer in overdose, had fewer drug interactions, and were efficacious in treating anxiety and insomnia. For a few years following their introduction, benzodiazepines were thought not to produce a dependence syndrome. It was soon discovered, however, that therapeutic doses could also lead to a withdrawal syndrome (Busto et al. 1986), and in animals, the benzodiazepine antagonist flumazenil could induce a withdrawal syndrome after a single dose of a benzodiazepine (Rosenberg and Chiu 1985). As clinical experience grew and other benzodiazepines were marketed, challenges to the safety of the class began to appear in the medical literature. Although some advantages of benzodiazepines over the older drugs remain unchallenged (e.g., greater safety in overdose when taken without other drugs), controversy persists regarding tolerance, dependence, abuse, and toxicity in long-term use.

Patterns of Use

Population Surveys

Since 1998 there has been a trend for increased drug mentions in emergency departments and an increase in their use with alcohol and other drugs in suicides. In young patients, misuse of benzodiazepines is secondary only to prescription pain relievers (Ciraulo 2014).

Medical Use

Reports of benzodiazepine abuse increased dramatically between 1969 and 1973, when they reached 87 million, then decreased to 61 million in 1987. Abuse reports stayed flat until 2002, when they began to increase again, rising to 74 million in 2007 and gradually returning to the early 1970 levels (Petursson and Lader 1981a, 1981b). The market share has shifted to shorter-acting agents (lorazepam and alprazolam) from the longer-acting benzodiazepines (diazepam and chlordiazepoxide), with the exception of clonazepam prescriptions, which have risen sharply from 2005 (National Center for Health Statistics 2011).

Most medical prescriptions for benzodiazepines are for short-term use of a month or less, with only 1% of patients taking them a year or longer (Lagnaoui et al. 2004; Olfson et al. 2004; Piper 1995; Veronese et al. 2007; Zandstra et al. 2002). Approximately 7.4%–17.6% of the general adult population reports taking a benzodiazepine for medical purposes at least one time in a given year, with 1% using the medication daily for a year or longer (Kranzler and Ciraulo 2005). Long-term users are more likely to be women, to be older, and to have chronic medical conditions and high levels of psychological distress (for review see Ciraulo and Oldham 2005).

Substance Use Disorders (Substance Abuse)

Despite the relatively low risk of benzodiazepine misuse in the medical setting, there are several groups of patients who are at high risk for abuse, and caution should be used when prescribing anxiolytics and hypnotics to these individuals. Heavy drinkers often present for treatment of anxiety and insomnia. Some of these individuals are reluctant to report

the quantity of alcohol consumed and may even deny drinking. When benzodiazepines are prescribed to these patients, there is a high likelihood of abuse. In such situations, when benzodiazepines are used to treat alcohol withdrawal symptoms, especially anxiety and insomnia, they serve as a priming drug to increase alcohol consumption or to enhance intoxication. Data from publicly funded addiction treatment centers (Substance Abuse and Mental Health Services Administration 2007) reported a disturbing trend: the percentage of benzodiazepines cited as the primary or secondary agent of abuse is increasing, especially in people age 55 years or older, although it is still low in comparison with alcohol and opioids. Whether benzodiazepines are primary or secondary has little effect on clinical management; the critical issue is that polysubstance abuse is the norm; frequently, benzodiazepines are among those drugs, and medical detoxification may be complicated by their use. Ten to twenty percent of patients entering treatment for alcoholism may be using or abusing benzodiazepines (Kranzler and Ciraulo 2005).

Methadone clinics report very high rates of benzodiazepine use detected in urine toxicology assessments. The benzodiazepines are used to self-medicate insomnia, anxiety, and withdrawal. They may also boost the hedonic effects of methadone.

Elderly Patients

Elderly patients have higher rates of medical use of benzodiazepines than younger individuals, although there is no evidence that misuse is higher in this group. The greatest concern for elderly patients receiving benzodiazepines is an increased risk of falls and cognitive impairment. With respect to falls, some studies have found that the selective serotonin reuptake inhibitors (SSRIs) and opioids present a greater risk of falls than benzodiazepines (Ensrud et al. 2003), which suggests that treatment of anxiety with SSRIs may also pose a risk to the elderly.

Chronic Pain

The Institute of Medicine reported that every year approximately 100 million adult Americans experience chronic pain (Institute of Medicine 2011). Somewhere between 40% and 60% of these patients receive benzodiazepines. With the exception of pain due to muscle spasms, currently marketed benzodiazepines do not have established efficacy for most pain conditions, but they may be helpful with anxiety, dysphoria, and sleep disturbances associated with chronic pain. Some experienced pain clinicians believe that the benzodiazepines may have a direct beneficial effect on neuropathic pain. The extent of misuse in this population is not well studied; however, one report found a rate of misuse of 3.2%–4.8% (Kouyanou et al. 1997).

Addictive Potential

The mood-elevating effect of benzodiazepines and barbiturates is probably mediated not only by acute increases in the actions of GABA but also by neural connections. Depletion of dopamine from the nucleus accumbens may attenuate the rewarding effects of diazepam (Spyraki and Fibiger 1988), as may the administration of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptor antagonists (Gray et al. 1999).

Pharmacodynamic tolerance to the psychomotor effects of benzodiazepines has been demonstrated after single or

multiple doses but is likely incomplete (File 1985; Greenblatt and Shader 1978; Rosenberg and Chiu 1985). Pharmacodynamic tolerance to the anxiolytic effect (over a 6-month period) has not been demonstrated (Rickels et al. 1983), and clinical experience supports the conclusion that many patients with anxiety disorders require long-term therapy with benzodiazepines or alternative antianxiety agents. Amnesic effects of benzodiazepines, especially the high-potency agents, persist during long-term therapy. Using the lowest possible doses of these drugs during periods when cognitive performance is critical (e.g., test taking) is a successful therapeutic strategy.

The extent to which tolerance develops to the actions of the Z drugs is not yet clear. The adverse effect of complex nocturnal behavioral toxicity appears more frequently with the Z drugs.

Several mechanisms have been implicated in the development of tolerance to benzodiazepines. These include down regulation of cortical benzodiazepine binding sites (Fahey et al. 2001), alterations in $GABA_A$ receptor subunit composition (Chen et al. 1999), and increased expression of AMPA (Allison and Pratt 2003; Van Sickle and Tietz 2002) and N-methyl-D-aspartate (Pérez et al. 2003) receptor subunits in the hippocampus.

Medical Consequences of Long-Term Use

There is no convincing evidence to suggest that there are irreversible adverse medical consequences of long-term benzodiazepine use. In one European study (Piesiur-Strehlow et al. 1986), the mortality rate among patients with isolated benzodiazepine dependence was greater than in the general population but equivalent to that in the control group (nondependent patients with comparable psychiatric illnesses). Virtually all of the medical morbidity and mortality was reported to have resulted from combination of benzodiazepines with other CNS depressants in individual occurrences; for example, a person chronically abusing diazepam in high doses who then drinks alcohol may encounter severe CNS depression resulting in respiratory depression or coma.

Anterograde amnesia has been well documented with a variety of benzodiazepines, and decrement in learning probably represents the single most significant drawback to medically indicated chronic use (Barker et al. 2004a; Curran 1986; Lister 1985; Vermeeren and Coenen 2011; Vermeeren et al. 1995). Most studies of cognitive function in long-term benzodiazepine use have demonstrated cognitive effects. A meta-analysis of 13 studies published between 1980 and 2000 found persistent deficits in long-term users compared with controls, especially in the areas of sensory processing, verbal reasoning, verbal memory, attention, and concentration (Barker et al. 2004b). One study reported that in a sample of individuals ages 60–70 years who were followed for 4 years, those taking benzodiazepines had a more rapid decline in cognitive function than those who were not taking benzodiazepines (Paterniti et al. 2002). Other studies, such as that of Puustinen et al. (2007), have found no difference in cognitive function in elderly long-term users of zopiclone, temazepam, and oxazepam and a group of nonusers. Most studies have found that discontinuation of benzodiazepines results in gradual improvement in cognitive function; however, the extent of recovery and the duration required to recover is not consistent in the literature (Barker et al. 2004b; Curran et al.

2003; Gallacher et al. 2012; Pat McAndrews et al. 2003; Salzman et al. 1992). Attempts to link benzodiazepines to dementia have been strongly criticized on scientific grounds (Billioti de Gage et al. 2012; Bocti et al. 2012, 2013; Coyle-Gilchrist 2012).

Clinical Management

Abstinence Syndrome

Smith and Wesson (1983) classified benzodiazepine withdrawal symptoms into *minor,* which includes anxiety, insomnia, and nightmares, and *major,* which includes seizures, psychosis, hyperpyrexia, and death. We have found a classification scheme based on temporal development more useful, categorizing withdrawal symptoms as *early, middle,* and *late.* The severity of symptoms progress with time, and the onset and duration of withdrawal depends on the elimination half-life of the parent benzodiazepine and active metabolites. *Early* symptoms include headache, dysphoria, mild anxiety, and difficulty falling asleep. *Middle* symptoms include myoclonic jerks (especially with clonazepam), insomnia, fatigue, diarrhea, difficulty concentrating, and exaggerated startle. *Late* symptoms include diaphoresis, tremulousness, fearfulness, paranoia, illusions, psychotic symptoms, hyperpyrexia, seizures, coma, and death. The objective of management of withdrawal is to relieve early symptoms and prevent progression to the late stage of withdrawal.

Protocols for Detoxification

The author's treatment approach to sedative-hypnotic withdrawal was first described in 1991 (Ciraulo and Shader 1991) and has had only minor modifications since then (Ciraulo 2014; Ciraulo and Knapp 2011; Ciraulo and Sarid-Segal 2009; Ciraulo et al. 2005; Oldham and Ciraulo 2011). Protocols described below are summarized from Ciraulo (2014).

Protocols for benzodiazepine detoxification vary on the basis of the following three categories: 1) patients who have been maintained on therapeutic dosages for moderate to long periods and for whom a trial off their medication is warranted, 2) patients taking supratherapeutic doses, and 3) patients who use benzodiazepines as part of mixed substance use disorder.

Therapeutic Doses

Detoxification can usually be accomplished using the same benzodiazepine that the patient is taking. Switching from a benzodiazepine with a short elimination half-life to one with a long elimination half-life may not be necessary if the tapering program is sufficiently long. If difficulty is encountered in tapering one benzodiazepine, however, then switching to one with a longer elimination half-life may be helpful. Substituting a medication with a shorter elimination half-life for one with a longer one is not advised (Conell and Berlin 1983). Approximate dosage equivalencies of benzodiazepines and sedative-hypnotics are listed in Tables 47–1 and Table 47–2, respectively.

We recommend an initial 10%–25% dose reduction, followed by careful observation of the patient for signs of the abstinence syndrome. Shorter elimination half-life agents (lorazepam, oxazepam) may have an earlier onset of symptoms, and withdrawal from longer half-life agents (clonazepam, diazepam) may not occur until several days after reducing the dose. Exceptions to this do occur—some patients seem exquisitely sensitive to the rate of decline of drug levels and may have abstinence symptoms in the

TABLE 47–1. Approximate benzodiazepine dose equivalency

Generic name	Brand name	Dose (mg)
Alprazolam	Xanax	1
Chlordiazepoxide	Librium	25
Clonazepam	Klonopin	0.5–1.0
Clorazepate	Tranxene	15
Diazepam	Valium	10
Flurazepam	Dalmane	30
Lorazepam	Ativan	2
Oxazepam	Serax	30
Temazepam	Restoril	20
Triazolam	Halcion	0.25
Eszopiclone	Lunesta	2
Zaleplon	Sonata	10
Zolpidem	Ambien	10

TABLE 47–2. Sedative-hypnotic dose equivalency

Older agents	Dose[a] (mg)
Secobarbital	100
Pentobarbital	60
Chlorate hydrate	250
Glutethimide	250
Meprobamate	200
Diazepam	5

[a]Equal to 30 mg of phenobarbital.

presence of therapeutic drug concentrations. Adjunctive medication is often used (see Table 47–3).

High Doses

Patients requiring detoxification from high or supratherapeutic doses of benzodiazepines constitute a smaller number of patients, but they are at greater risk for life-threatening discontinuation symptoms such as seizures, delirium, and psychoses. There has been more experience with inpatient detoxification in this group, but recent restrictions in reimbursement for inpatient treatment in the United States have led to increasing use of combinations of outpatient and residential settings for detoxification. Outpatient detoxification is possible if conducted slowly (no greater than 5% reduction per week), with frequent contact to monitor for early abstinence symptoms. In a high percentage of these patients, inpatient treatment may be required. Patients with a history of seizures, delirium, or psychoses during previous detoxification attempts should be admitted for inpatient detoxification.

In high-dose detoxification, avoiding major adverse consequences requires that a smooth decline in plasma benzodiazepine levels be achieved. Here, switching to diazepam or another long-acting benzodiazepine is recommended. Patients should be switched to an equivalent dose of long-

TABLE 47–3. Adjunctive medications used in the treatment of benzodiazepine withdrawal

Medication class	Medication
α_2 Receptor agonists	Clonidine
Anticonvulsants	Carbamazepine, valproic acid, gabapentin, pregabalin, topiramate
Antidepressants[a]	Trazodone; mirtazapine; paroxetine, other selective serotonin reuptake inhibitors; venlafaxine
β Receptor antagonists	Propranolol, others
Serotonin$_{1A}$ receptor (5-HT$_{1A}$) agonists	Buspirone[b]

Note. Efficacy of these agents is not established.
[a]Sedative antidepressants are used in acute withdrawal; antidepressants with antianxiety actions are used for long-term discontinuation.
[b]Buspirone is not cross-tolerant to benzodiazepines and should not be used for acute withdrawal; high doses may be used to treat anxiety disorders to help maintain long-term discontinuation after abstinence has been achieved.

acting benzodiazepine given in divided daily doses (see Table 47–1) and stabilized on this dosage for the first day (some clinicians stabilize for 2–3 days). Following stabilization, a 30% cut is made in the dose on day 2 (or on days 3–4 if a longer stabilization period is used) followed by a 5% cut on each day thereafter. This will result in complete detoxification in about 2 weeks for patients who have been using high doses for a period of 3 months or less. Longer-term use will require an initial reduction of 10%–20% followed by 5% cuts every 1–2 weeks. The rate of tapering must be individualized and should be slowed even further in the presence of diaphoresis, tremulousness, or elevated vital signs. Hyperpyrexia is a grave sign and should prompt aggressive management and inpatient admission. Supplemental benzodiazepine and supportive medical care are necessary in these instances. This protocol should serve only as a guideline because individual patients will vary in their sensitivity to withdrawal. True withdrawal is best distinguished from recurrence of anxiety by the development of new symptoms and/or the appearance of perceptual disturbance (e.g., ringing in ears, sensitivity to sounds, and dizziness). Whenever possible, doses should be adjusted to keep patients comfortable. Adjunctive medications can be used as described below. Close monitoring for the week following detoxification is prudent because some symptoms may not be evident until then as the desmethyldiazepam and other metabolite levels continue to fall.

Benzodiazepines in Mixed Substance Use Disorder

Sporadic use (as in the induction of sleep following a psychostimulant binge) does not require specific detoxification. Sustained use can be treated as described earlier for low or high doses but with added caution. In mixed opioid and benzodiazepine abuse, the patient should be stabilized on methadone (some clinicians use other oral preparations of opioids) and a benzodiazepine. Buprenorphine should be administered cautiously with benzo-

diazepines because a pharmacodynamic interaction is possible and fatalities have been reported with the combination (Ibrahim et al. 2000; Kilicarslan and Sellers 2000; Reynaud et al. 1998), although we have treated many patients who have tolerated therapeutic benzodiazepine doses. For patients who are misusing several different anxiolytics and hypnotics (e.g., benzodiazepines, barbiturates, ethanol, and propanediols), most often adequate coverage can be achieved by a single medication, and a benzodiazepine is probably the safest choice; however, some experienced clinicians prefer barbiturates (phenobarbital) in these cases.

Adjunctive Medication Strategies

Adjunctive medications that may be of value in the management of benzodiazepine withdrawal are listed in Table 47–3. The two major roles for adjunctive medication are to reduce acute withdrawal symptoms and to maintain long-term discontinuation. Although neither approach is well studied, clinical experience suggests that adjunctive medications are of value in acute withdrawal. Long-term discontinuation depends on many factors, such as psychiatric diagnosis, personality traits, and the efficacy of alternative agents in treating anxiety (e.g., antidepressants).

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CHAPTER 48

Opioid-Related Disorders: Opioid Detoxification

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Opioid detoxification is a preparatory phase of treatment focused on ridding the body of opioids and overcoming physical dependence before hopefully beginning a longer-term abstinence-based treatment. However, some individuals will begin detoxification to decrease the cost of their habit without intending to remain abstinent. For individuals seeking treatment, current evidence favors the use of agonist maintenance therapies for opioid use disorder; however, detoxification can be appropriate for some highly motivated individuals who do not want to be physically dependent on opioids and who have a strong support network. Other factors favoring detoxification are limited access to agonist therapies or a desire for residential treatment where agonist medications are typically not available. Successful detoxification is related more to the reason for detoxification than to the methods. Methadone, buprenorphine, and clonidine are well-established medications used in detoxification.

Setting Choice

Detoxification can be conducted in inpatient, outpatient, or partial hospitalization settings. Outpatient detoxification has become increasingly common since the advent of buprenorphine office-based treatment. It is less expensive, and patients may be able to continue to work. However, the risk for relapse may be greater given patients' access to drugs at a time when cravings can be high. Inpatient detoxification limits access to drugs and craving-inducing stimuli, allows for medical monitoring, and can shorten the acute withdrawal phase. However, it is expensive and disruptive to the individual's work and home life. Partial hospi-

talization programs are less expensive than inpatient programs, but they are not widely available.

Clinical Characteristics of the Opioid (μ Agonist) Withdrawal Syndrome

Physiological dependence warranting detoxification usually develops after daily use of opioids for a period of at least 2–3 weeks, though previously dependent individuals may develop dependence more quickly. Opioid withdrawal on its own is not life threatening, but it is extremely unpleasant, and without treatment, individuals experience strong cravings for opioids to relieve the discomfort.

Factors Influencing Symptom Severity

Longer-acting opioids will lessen the intensity but increase the duration of withdrawal symptoms relative to shorter-acting opioids. In general, the larger the amount used per day, the more severe the withdrawal, though some evidence suggests that dosage does not correlate with symptom severity (Gossop et al. 1987). Similarly, duration of use beyond 2–3 months does not worsen withdrawal. Individual patient factors, such as personality, motivation, stress tolerance, physical health, and psychological state, can all influence withdrawal severity.

Signs and Symptoms of Opioid Withdrawal

The μ agonist withdrawal syndrome can be conceptualized as rebound hyperactivity in the biological systems suppressed by opioid agonists. The withdrawal symptom profile is the opposite of the agonistic effects (e.g., opioid agonists cause myosis, and mydriasis presents in withdrawal).

Withdrawal from short-acting opioids such as heroin typically begins 8–10 hours after the last dose and reaches its peak 36–72 hours later, subsiding within about 5 days. It begins with anxiety and craving and progresses to yawning, rhinorrhea, lacrimation, perspiration, restlessness, and disrupted sleep (Table 48–1). Later, hot and cold flashes, body aches, muscle twitching, and gastrointestinal symptoms emerge. Onset from methadone withdrawal begins at 24–36 hours, peaks between days 4–6, and subsides 14–21 days later (Kleber 1996).

Following the acute phase of opioid withdrawal, protracted subacute symptoms typically persist for 6 months or longer. These symptoms include general malaise, fatigue, irritability, dysphoria, and insomnia. Cravings for opioids can be strong, which may increase the risk of relapse (Satel et al. 1993).

Opioid Agonist Substitution and Tapering

Cross-tolerance between opioids allows almost any opioid to be used to detoxify dependent individuals. Most of the time, buprenorphine or methadone will be used, or the narcotic can be tapered off. However, one should avoid using a more addictive drug in detoxification, such as methadone for tramadol dependence. At high doses, tramadol has enhanced opioid effects (Duke et al. 2011) and thus more addictive potential than previously thought. However, given that these effects are weaker at lower doses, detoxification using buprenorphine or tapering off the tramadol is safer than using methadone.

TABLE 48–1. Signs and symptoms of opioid withdrawal

Early to intermediate	Intermediate to advanced
Anxiety, dysphoria, irritability	Abdominal cramps
Craving	Disrupted sleep
Restlessness	Hot and cold flushes
Anorexia, nausea	Increased blood pressure, heart rate
Fatigue	Low-grade fever
Headache	Muscle and bone aches, muscle twitching
Increased respirations	Mydriasis (dilated and fixed)
Lacrimation, rhinorrhea, yawning	Diarrhea, possibly vomiting
Mydriasis (mild)	

Methadone

Methadone is given orally and is long acting, allowing for once daily dosing and a milder, albeit longer, course of withdrawal. Methadone is a safe and effective means of detoxification if care is taken with the initial dosing.

The first dose should not exceed 30 mg because higher doses can be fatal in nontolerant individuals. An exception is if the patient has well-documented or observed tolerance to narcotic medications that can be converted into an approximate equivalent methadone dose (Table 48–2). With illicit drug use, dosage is not reliable for conversion into methadone dose equivalents.

A starting dose of 10–20 mg will suppress withdrawal symptoms for many opioid habits but is safe for virtually everyone. The patient should be observed to assess the effect of the first dose and monitored for drowsiness and respiratory depression. Withdrawal symptoms will be reduced within 60 minutes and will be significantly decreased 2–4 hours later as methadone reaches its peak effect. If symptoms persist 1–2 hours after the initial dose, another 5–10 mg can be given. In inpatient settings, split dosing (10–20 mg every 12 hours) can prevent withdrawal symptoms that emerge when a 24-hour dose wears off. The total dose should be less than 40 mg per 24 hours for the first few days because doses that are well tolerated initially can become dangerous after 1–2 days as methadone accumulates and the levels rise in the blood (Dart et al. 2005). Steady state blood levels can take up to 5 days or more to achieve.

The total dose given on day 1 should be repeated on day 2, with adjustment for sedation or residual withdrawal. Increases should be made on the basis of objective signs of withdrawal, such as dilated pupils, rather than the patient's subjective symptoms. After the patient is stabilized, the dose is tapered by 5–10 mg per day until the last 10 mg, when the dose is reduced more slowly (by 2 mg/day). Inpatient methadone detoxification can be done within 3–7 days, but outpatient tapers are done over weeks to months in order to minimize withdrawal and decrease the likelihood of dropout.

Patients coming off of methadone maintenance ideally have the methadone tapered over 3–6 months, with doses

TABLE 48–2. Duration of action and course of withdrawal

Drug	Duration of effects[a] (hours)	Appearance of withdrawal (hours)	Peak withdrawal effects (hours)	Resolution of acute withdrawal
Fentanyl[b]	1	3–5	8–12	4–5 days
Meperidine	2–3	4–6	8–12	4–5 days
Oxycodone[c]	3–6	8–12	36–72	7–10 days (approximately)
Hydromorphone	4–5	8–12	36–72	7–10 days (approximately)
Heroin	4	8–12	36–72	7–10 days
Morphine	4–5	8–12	36–72	7–10 days
Codeine	4	8–12	36–72	7–10 days (approximately)
Hydrocodone	4–8	8–12	36–72	7–10 days (approximately)
Methadone	8–12	36–72	96–144	14–21 days
Buprenorphine	24–36	72	72–120	8–10 days

[a]Duration is based on acute doses; chronic dosing can vary.
[b]Intravenous effects are described; transdermal fentanyl can take 16–24 hours to appear because of continued absorption through the skin after the patch is removed.
[c]Effects of short-acting agents are described; long-acting oral form may last up to 12 hours.

decreased by 5–10 mg/week. When the daily dose reaches 25 mg, withdrawal symptoms may emerge in less than 24 hours, at which point the dose should be decreased by 5 mg/week or less. Split doses can help if they are feasible.

Methadone toxicity manifests as myosis, mild hypothermia, nausea, and motor impairment and can progress to respiratory depression. Methadone carries a black box warning for QT prolongation; the QT interval should be monitored in patients with risk factors, including concurrent use of other drugs that may also have this effect and act synergistically (e.g., antipsychotics). Naloxone hydrochloride 0.4–0.8 mg can reverse toxicity, usually in repeated doses because of its short duration of action and methadone's long half-life (Chhabra and Bull 2008).

Buprenorphine

Buprenorphine is a partial μ receptor agonist and κ receptor antagonist. It is available in a sublingual formulation as buprenorphine alone (Subutex) or with naloxone (Suboxone) in a 4:1 buprenorphine-naloxone ratio. Naloxone has minimal bioavailability sublingually and was added to reduce the risk of buprenorphine abuse. It was previously thought that crushed Suboxone used intranasally or parenterally would precipitate withdrawal; however, when tested in a randomized controlled trial with intravenous drug users, self-administered intravenous Suboxone did not induce aversive withdrawal effects. Intravenous Suboxone was shown to have less positive subjective effects and a lower abuse potential relative to heroin and buprenorphine, especially in individuals maintained on higher doses of buprenorphine (24 mg) relative to those on lower doses (2 mg) (Comer et al. 2010). In 2012, Reckitt-Benckiser stopped producing tablets and began manufacturing Suboxone as an individually wrapped sublingual strip, citing reduced overdose potential in children with this formulation.

Buprenorphine is long acting, safe, and effective when given orally. Because it is a partial μ agonist with high receptor affinity, it can precipitate withdrawal if given too soon after use of an opioid agonist. Clinicians should wait until mild to moderate withdrawal symptoms are present, usually 12–18 hours after last use of short-acting opioids and/or corresponding to scores of 10–12 on the Clinical Opioid Withdrawal Scale (COWS; Wesson and Ling 2003). A first dose of 2–4 mg can be repeated 1 hour later depending on the effect. Buprenorphine is titrated up to 8–16 mg/day until withdrawal symptoms are suppressed, and then the drug is typically tapered over 7–14 days and discontinued (Amass et al. 2004; Ling et al. 2005). However, some evidence exists of successful detoxification lasting less than a week (Lintzeris 2002; Lintzeris et al. 2002).

Withdrawal from stopping buprenorphine varies among individuals and likely depends on the dosage (Fudala et al. 1990; Mello and Mendelson 1980). Buprenorphine has significantly less risk for toxicity than methadone because it is a partial agonist. However, deaths from respiratory depression have been reported, usually occurring with use or abuse of sedatives such as benzodiazepines and neuroleptics (Kintz 2002; Mégarbane et al. 2006; Reynaud et al. 1998).

Buprenorphine can be used for detoxification from methadone. Tapering methadone to less than 40 mg/day before giving buprenorphine can reduce withdrawal. Clinicians should use the COWS to assess the presence of mild to moderate withdrawal and wait a minimum of 36 hours after the last dose of methadone before beginning buprenorphine.

Other Detoxification Agents and Methods

Clonidine

Clonidine, an α_2-adrenergic agonist, can mitigate opioid withdrawal symptoms by reducing the central and peripheral sympathetic activation response. It can lessen tachycardia, hypertension, sweating, and hot and cold flushes, and its sedating effects can reduce anxiety, restlessness, and agitation. It is not effective in relieving craving, restlessness, or body aches (Charney and Kleber 1980; Jasinski et al. 1985; Kleber et al. 1985). Although clonidine is a sedating medication, insomnia is also a side effect, and thus, clonidine can exacerbate insomnia during withdrawal.

Clonidine can be started immediately after opioids are stopped. Inpatients have been abruptly switched from 50 mg of methadone to clonidine with success. Clonidine is started at 0.1–0.2 mg every 4–6 hours; individuals with dependence on short-acting opioids may tolerate higher daily doses and require a course of treatment. In precipitated withdrawal or antagonist induction, which induces a hypertensive state, doses as high as 2.5 mg/day can be given with monitoring of heart rate and blood pressure to minimize the risk of hypotension and syncope. Blood pressure is checked before each dose, and clonidine is held for pressures less than 100/55.

Clonidine detoxification can also be done in outpatient settings. Outpatients taking methadone 20 mg/day who were switched to clonidine did as well as those undergoing a methadone taper of 1 mg per day (Kleber et al. 1985). Patients should be given no more than a 2-day supply of clonidine, and they should be told not to drive. Blood pressure should be checked at every visit. Patients should drink fluids, lie down, and reduce their dose if they feel dizzy.

Other Alpha$_2$-Adrenergic Agonists

Lofexidine and Guanfacine

Multiple clinical trials have found lofexidine to be an effective treatment for opioid withdrawal comparable to clonidine. It causes less hypotension than clonidine (Gish et al. 2010) but can adversely affect cardiac conduction. However, it is not currently available in the United States. Guanfacine has been studied much less, and evidence is insufficient to determine its utility in treating opioid withdrawal. The α_2 agonists mitigate withdrawal symptoms, but outcomes of detoxification with clonidine alone are less favorable than those with methadone or buprenorphine (Gowing et al. 2009a; Meader 2010). In clinical practice, α_2 agonists are most commonly used in combination with other agents.

Naltrexone

Using the opioid receptor antagonist naltrexone in detoxification precipitates withdrawal and hastens detoxification. Initiating naltrexone during detoxification can also facilitate the transition to antagonist maintenance therapy, if that is desired.

Naltrexone is frequently combined with buprenorphine and/or clonidine (Kosten and O'Connor 2003; O'Connor et al. 1997; Sigmon et al. 2012; Stine and Kosten 1992) to attenuate the severe withdrawal symptoms caused by naltrexone's abrupt displacement of opioids from receptors. One strategy involves using low doses of buprenorphine, such as 4–8 mg, on day 1, then starting naltrexone

at a dose of 12.5 mg per day on day 3. If severe withdrawal is expected, naltrexone can be delayed until day 4 or 5 and started at 3 mg twice a day. Clonidine and adjunctive medications are used throughout. Naltrexone is titrated up to 25–50 mg and continued through detoxification. This approach can decrease withdrawal by first transitioning the patient from full to partial agonist before giving naltrexone (see Sigmon et al. 2012). Recent evidence suggests that very low doses of naltrexone (0.125 and 0.25 mg/day) may be a beneficial adjunct to detoxification with methadone (Mannelli et al. 2009). However, naltrexone is not currently available in these doses, and further investigation of this combination and other regimens is needed.

In rapid detoxification, patients stop opioids and are treated with oral naltrexone on day 1, along with clonidine and ancillary medications (Riordan and Kleber 1980). However, rare but severe withdrawal symptoms and potentially dangerous side effects (delirium, dehydration, hypotension, hypovolemic shock), can result (Gowing et al. 2009b), and medical monitoring on an inpatient detoxification unit is needed. Ultrarapid detoxification using high-dose antagonists while patients are under general anesthesia or heavy sedation is not recommended. The risk of life-threatening adverse events cannot be justified when evidence does not demonstrate better outcomes (Collins et al. 2005; Favrat et al. 2006; Gowing et al. 2010).

Other Drugs and Supportive Measures

Medications commonly used to address insomnia in opioid withdrawal include trazodone (50–100 mg), quetiapine in low doses (25–100 mg), and sedative-hypnotic agents (e.g., zolpidem 10 mg or eszopiclone 3 mg). Benzodiazepines (e.g., clonazepam, oxazepam, lorazepam) and antihistamines (e.g., diphenhydramine 50 mg every 4–6 hours) can simultaneously reduce insomnia and relieve anxiety and restlessness. The dosages of benzodiazepines will vary depending on the patient's tolerance and symptoms (e.g., clonazepam 0.5–2 mg every 4–8 hours, 6 mg/day maximum). Benzodiazepines and sedative-hypnotic agents are safe for use in inpatient settings but should be used cautiously in outpatient settings where the medication is not controlled.

Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen 600–800 mg every 6–8 hours) can reduce muscle and joint pain. For patients unable to tolerate oral medications, ketorolac 30 mg every 6 hours can be given acutely. Antispasmodics such as cyclobenzaprine (5–10 mg every 8 hours) can reduce muscle cramping. Antiemetics such as ondansetron (8 mg every 8–12 hours) help reduce nausea and can be given parenterally if needed. For diarrhea, loperamide or bismuth subsalicylate can be given after each loose stool. Oral hydration with electrolytes is encouraged, and backup intravenous hydration should be available. Patients should get a multivitamin with minerals. Warm baths, light exercise, acupuncture (Liu et al. 2009), electric acupoint stimulation (Meade et al. 2010), and qigong (Li et al. 2002) may also be beneficial in detoxification.

Special Problems

Pain

Patients with pain need to be counseled that their pain may temporarily worsen during the acute withdrawal period. For acute pain, it is best to wait until the pain is manageable with nonsteroidal anti-inflammatory drugs before starting de-

toxification. For patients with chronic pain, Suboxone maintenance is an alternative to detoxification used in clinical practice. Many patients with chronic pain have hypersensitization to pain and opioids, and their pain will improve following detoxification. Clinicians should collaborate with the patient and other treating clinicians to have a comprehensive plan for pain management in place before beginning detoxification.

Pregnancy and Neonates

Detoxification poses significant risks in pregnancy. Relapse is common and subjects the fetus to periods of intoxication and withdrawal, which increases the risk of miscarriage, stillbirth, prematurity, and possible developmental abnormalities. Risk is compounded by poor prenatal care, malnutrition, and possible drug adulterants. Agonist maintenance therapy with methadone or buprenorphine (without naloxone) is recommended, and recent evidence suggests better fetal outcomes with buprenorphine (Jones et al. 2010). If detoxification is undertaken, it should be done in the second trimester to minimize the risk of miscarriage or premature delivery. Methadone should be tapered no more than 5 mg/week. Naltrexone is not recommended during pregnancy because of increased risk of miscarriage and premature delivery. Neonates dependent on opioids should be tapered slowly to prevent neonatal abstinence syndrome. Typically, morphine is used, but recent evidence supports the use of buprenorphine as safe and effective with shorter hospitalizations (Kraft et al. 2008, 2011).

Mixed Addictions

Individuals dependent on sedative-hypnotics (e.g., alcohol, benzodiazepines, and barbiturates) are at risk for seizures, delirium, and even death. When dependence on both opioids and sedatives co-occurs, it is best to treat the opioid dependence with agonist maintenance therapy and completely withdraw the sedative first. Risk is less for patients dependent on stimulants and opioids, though severe depression can result and suicide is possible.

Seizure, Vomiting, and Medical Comorbidities

Seizures do not typically occur in opioid withdrawal or intoxication. When seizures do occur, they may signal alcohol or sedative withdrawal or stimulant intoxication or may be related to a comorbid medical condition. Vomiting may be withdrawal related or related to treatment with opioid agonists. Intramuscular or parenteral antiemetics and intravenous hydration may be necessary acutely. Opioid withdrawal may cause low-grade fever (less than 100.4°F or 38°C). In acute febrile illnesses, withdrawal can worsen, and more methadone may be needed. When serious medical or surgical problems are present, withdrawal should be delayed or done very gradually to minimize stress on the body; in certain medical conditions (e.g., myocardial infarction) the patient should continue agonist therapy until stabilized.

Conclusion

For most individuals with opioid dependence, detoxification is the first step in a long process of maintaining abstinence. Success is a function of comfort and safety of the opioid withdrawal but also of retention in detoxification and longer-term treatment. Office-based buprenorphine treatments have increased the availability, safety, and comfort of opioid detoxification.

Useful Web Sites

American Academy of Addiction Psychiatry: www.aaap.org

American Psychiatric Association: www.psych.org

Narcotic Equivalence Converter: http://www.medcalc.com/narcotics.html

Overview of the Patient Placement Criteria, Substance Abuse and Mental Health Services Administration: http://www.samhsa.gov/co-occurring/topics/screening-and-assessment/asam-overview.aspx

Substance Abuse and Mental Health Services Administration: www.samhsa.gov

Treatment Improvement Protocol (TIP) 45: Detoxification and Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration: http://store.samhsa.gov/product/TIP-45-Detoxification-and-Substance-Abuse-Treatment/SMA13-4131

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CHAPTER 49

Opioid-Related Disorders: Antagonist Treatment

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For the treatment of opioid use disorder, agonists and partial agonists such as methadone and buprenorphine have had the most impact. They attach to opioid receptors and stimulate them. They are effective for the treatment of opioid use disorder mainly because they reduce opioid withdrawal symptoms, reduce opioid craving, and confer tolerance to opioids (methadone) or block opioid receptors (buprenorphine), thus reducing the euphoric effects of abused opioids. However, opioid antagonists such as naltrexone are also available for the treatment of opioid dependence. Naltrexone occupies opioid receptors but does not activate them; because naltrexone has a high affinity for the opioid receptor, it can prevent agonists with lower affinity such as heroin from binding with the receptor and thus reduce the euphoric effects of abused opioids. Although naltrexone cannot treat opioid withdrawal, it has been shown to reduce opioid craving, and thus, for detoxified patients with opioid use disorder, it may provide an alternative to methadone and buprenorphine for the treatment of that disorder.

In this chapter we provide a review of the evidence supporting the usefulness of naltrexone for the treatment of opioid use disorder in both its oral form and its injectable or implantable forms. Safety questions in the use of naltrexone are discussed, and finally, ways that naltrexone can be integrated into a comprehensive treatment program are presented.

Naltrexone Pharmacology

Antagonists such as naltrexone bind to opioid receptors, but they do not activate the receptor to initiate the chain of cellular events that produce so-called opioid effects. Naltrexone is a relatively pure antagonist in that it produces little

or no agonist activity at usual doses. Not only do pure antagonists fail to produce opioid effects but their presence at the receptor also prevents opioid agonists from binding to the receptor and producing opioid effects. Because the antagonist competes for a binding site with the agonist, the degree of blockade depends on the relative concentrations of each and their relative affinity for the receptor site. Naltrexone has high receptor affinity, and thus, it can block virtually all the effects of the usual doses of opioids and opiates. In the presence of naltrexone, there can be no opioid-induced euphoria, respiratory depression, pupillary construction, or any other opioid effect (O'Brien et al. 1975).

Naltrexone is well absorbed orally, and it has a long duration of action. In the presence of naltrexone, heroin self-administration is no longer rewarding, and under experimental conditions, addicted individuals stop taking heroin even when it is available (Mello et al. 1981). Although daily ingestion of naltrexone would provide the most secure protection against opioid effects, naltrexone can be given as infrequently as two or three times per week, with adequate protection against readdiction to street heroin. In human laboratory trials, oral naltrexone given at a dose of 100 mg was able to block 96% of the subjective effects of a 25 mg dose of heroin at 24 hours and 87% of the effects at 48 hours (Verebey 1981). In part on the basis of the results of this trial, many clinicians will dose naltrexone three times weekly: 100 mg on Monday and Wednesday and 150 mg on Friday. The reduced frequency makes monitoring of the medication more practical over the long term. Tolerance does not appear to develop to the antagonism of opioid effects even after more than 1 year of regular naltrexone ingestion (Kleber et al. 1985).

Oral Naltrexone

Efficacy

Naltrexone was approved by the U.S. Food and Drug Administration (FDA) on the basis of its clear pharmacological activity as an opioid antagonist. Among patients with opioid dependence in general, oral naltrexone has not been shown to be consistently efficacious (Adi et al. 2007; Minozzi et al. 2011). However, among certain populations and under certain conditions, oral naltrexone may be effective.

Patients with a history of recent employment and good educational backgrounds do well when taking naltrexone. Some patients avoid methadone because of the required daily clinic visits, especially at the beginning of treatment. Because naltrexone is not a controlled substance, greater flexibility is permitted, and it can be prescribed from any physician's office. Although high-functioning patients may be strongly motivated to be drug free, they remain susceptible to impulsive drug use. Using naltrexone as a kind of "insurance" is often a very appealing idea.

Health care professionals generally have done well in naltrexone treatment programs. For example, Ling and Wesson (1984) reported the use of naltrexone in the management of 60 health care professionals for an average of 8 months. Forty-seven (78%) were rated as "much improved" or "moderately improved" at follow-up. Washton and colleagues (1984) found that 74% of physicians with opioid dependence completed at least 6 months of treatment with naltrexone and were opioid free and practicing medicine at 1-year follow-up. Roth and colleagues (1997) reported on the use of naltrexone in a specialized treatment program for

health care professionals addicted to opioids. This program combined supervised naltrexone administration and group therapy. In a sample of 18 subjects, 94% achieved long-term abstinence. These studies involved comprehensive treatment programs, with naltrexone providing a kind of structure around which psychotherapy was built.

Washton and colleagues (1984) reported on the treatment with naltrexone in 114 businessmen dependent for at least 2 years on heroin, methadone, or prescription opioids. A critical feature of this group was that there was considerable external pressure for them to receive treatment, and almost half were in jeopardy of losing their jobs or facing legal consequences. Of the entire group, at 12–18 month follow-up, 64% were still opioid free. Those patients who had stipulated pressure from their employers to get treatment did significantly better than the group without a clear-cut risk of job loss.

Another population that has done well with naltrexone is probationers who face a return to prison if they return to opioid use. Cornish and colleagues (1997) conducted a random assignment study among federal probationers convicted of drug-related crimes in Philadelphia, Pennsylvania. The probationers all received the same amount of parole counseling, but half were randomly selected to receive naltrexone. At follow-up 6 months after leaving prison, the group randomly selected for naltrexone had approximately half the reincarceration rate of the control group. More recently, an attempt to replicate these findings in a larger and more diverse group of probationers was only partially successful. In this trial, high dropout rates in both groups resulted in no overall effect. However, in a subset of probationers with high levels of supervision in a drug court setting, 57% of the naltrexone-treated probationers completed treatment, whereas none of the treatment-as-usual probationers did so (Coviello et al. 2010).

Problems With Oral Naltrexone

A major impediment to the more widespread use of oral naltrexone is the early dropout rate and poor medication compliance. Patients are often ambivalent about treatment or are forgetful, and a long-acting medication would eliminate the need to remember to take a medication daily. In a review of trials of oral naltrexone, the average retention rate at 26 weeks was 31% (Adi et al. 2007). In a 12-week trial of oral naltrexone conducted in patients addicted to heroin, more than half the subjects were dropped from the trial because of treatment noncompliance (Tucker et al. 2004). Because naltrexone is an opioid antagonist, use of naltrexone rapidly decreases tolerance to opioids, resulting in an increased risk of overdose in patients treated with naltrexone (Miotto et al. 1997; Ritter 2002). In some studies, mortality rates associated with oral naltrexone use have been shown to be higher than those associated with heroin use or with agonist treatment (Gibson and Degenhardt 2007). Among patients with low motivation for treatment and especially in treatment settings that cannot guarantee adherence, oral naltrexone is likely to be ineffective and may be dangerous.

Implantable and Injectable Naltrexone

Because of the high dropout rate and poor compliance associated with oral naltrexone, longer-acting implantable and injectable forms of naltrexone have been developed. These forms of naltrexone

have been shown to provide adequate naltrexone blood levels in the 1–2 ng/mL range for up to 3–6 months in the implantable forms and up to 30 days in the injectable form. Only the injectable form of long-acting naltrexone (Vivitrol) has been approved by the FDA for the treatment of opioid dependence.

Implantable forms of naltrexone have been developed in the United States and Australia. The chief advantage of these forms of naltrexone is that they provide therapeutic levels of naltrexone for a long period of time, up to 6 months in some of the implants. In controlled trials, implantable naltrexone has been shown to be superior to treatment as usual, oral naltrexone, and placebo for the treatment of opioid dependence and superior to placebo for the treatment of combined opioid and amphetamine dependence. Kunøe and colleagues (2009) compared naltrexone implants to treatment as usual in 56 detoxified patients with opioid dependence in a 6-month trial. Naltrexone-treated patients had, on average, 45 days less heroin use and 60 days less opioid use than patients receiving only psychosocial treatment. In another trial, naltrexone implants were compared with oral naltrexone in 70 patients with heroin dependence (Hulse et al. 2009). Patients were randomly assigned to either active implants and placebo oral naltrexone or placebo implants and active oral naltrexone. More subjects treated with naltrexone implants maintained therapeutic naltrexone levels compared with subjects treated with oral naltrexone. Patients treated with oral naltrexone were more likely than patients treated with implants to return to regular heroin use by 6 months. The implants were noted to be safe and well tolerated. More recently, Krupitsky and colleagues (2012) evaluated the efficacy of naltrexone implants versus oral naltrexone and placebo in a 6-month double-blind, double-dummy placebo-controlled trial involving 306 patients with opioid addiction. In this trial, there were three groups: one group received naltrexone implants and oral placebo, one group received placebo implants and oral naltrexone, and one group received placebo implants and oral placebo. The primary outcome was retention in treatment without relapse to opioid use. Naltrexone implants were significantly better than oral naltrexone and placebo implants in preventing relapse. Of the patients treated with naltrexone implant or oral placebo, 52.9% completed the 6-month trial without relapse, compared with 15.7% of the oral naltrexone or placebo implant group and 10.8% of the placebo implant and oral placebo group. Finally, naltrexone implants were found to reduce opioid and amphetamine use in patients addicted to both drugs (Tiihonen et al. 2012). In this trial, 100 patients addicted to opioids and amphetamines were randomly assigned to receive either naltrexone implants or placebo implants for a 10-week trial. At 10 weeks, the retention rate and the percentage of drug-free urine samples were greater in the naltrexone implant group compared with the placebo implant group (52% versus 28% retention and 38% versus 16% drug-free urine samples). Naltrexone implants have demonstrated efficacy for the treatment of opioid dependence and may also have efficacy for the treatment of combined opioid and amphetamine dependence.

Injectable naltrexone has also shown efficacy for the treatment of opioid dependence in two trials. In one small trial, injectable naltrexone was shown to be more efficacious than placebo injections (Comer et al. 2006). This trial lasted 8 weeks and involved 60 patients dependent on heroin. Patients were randomly assigned to one of two doses of injectable naltrex-

one (192 or 384 mg) or a placebo injection. Injections were given twice, 4 weeks apart. Time to dropout was significantly longer in the higher dose of naltrexone compared with placebo. When missing urine samples were coded as positive, the percentage of opioid negative samples was significantly higher in the two naltrexone groups compared with placebo: 61.9% negative in the patients treated with 384 mg/dose, 47.1% negative for patients receiving 192 mg/dose, and 25.3% negative for patients receiving placebo (Comer et al. 2006). In a much larger multicenter trial conducted in Russia, Krupitsky and colleagues evaluated another form of injectable naltrexone (Krupitsky et al. 2011). This trial ultimately led to FDA approval of extended-release injectable naltrexone (XR-NTX) for the treatment of opioid dependence. This trial involved 250 patients with opioid dependence randomly assigned to receive six monthly injections of either XR-NTX or placebo. The median proportion of weeks of confirmed abstinence was significantly higher in the XR-NTX group compared with the placebo group (90% versus 35%). Retention rates were significantly lower, and opioid craving was rated significantly less in the XR-NTX group compared with the placebo group. The injections were well tolerated.

The safety of implantable and injectable naltrexone is supported by the results of the clinical trials in which the implants and injections were administered safely and were well tolerated (Comer et al. 2006; Krupitsky et al. 2011, 2012). Questions regarding increased mortality associated with implantable naltrexone have been addressed in two trials. In one trial, Tait and colleagues compared mortality in heroin users 3 years after naltrexone implant or methadone maintenance treatment in Australia (Tait et al. 2008). They found that overall mortality rates were similar between the two groups. In a more recent trial, Kelty and Hulse (2012) found that during the first 4 months of treatment, overall mortality rates and rates of opioid overdose were lower in patients treated with naltrexone implants compared with patients treated with placebo. The data suggest that implantable naltrexone treatment may be as safe as methadone maintenance and may be safer than treatment with oral naltrexone.

Use of Naltrexone in a Comprehensive Treatment Program

Naloxone Testing for Residual Dependence

Various methods are available for beginning treatment with naltrexone. In all cases, there should be no residual physical dependence on opioid agonists. If the patient has been using a long-acting opioid such as methadone, it may be necessary to wait 7–10 days after the last dose before treatment with naltrexone is initiated. With dependence on short-acting drugs such as heroin or oxycodone, the time between detoxification and starting naltrexone can be much shorter. If naltrexone is started too soon, precipitated withdrawal will occur. Even mild withdrawal, consisting of only abdominal cramps or periods of nausea, may be enough to discourage the patient from further treatment.

Most clinicians who work with naltrexone have found it helpful to administer a naloxone challenge test to determine whether the patient has any residual physical dependence before he or she is given the first dose of naltrexone. A positive test indicating physical dependence

consists of symptoms of opioid withdrawal, such as perspiration, nausea, or cramps, that last for 20–40 minutes. A positive test indicates that the patient should wait at least another day before starting naltrexone. Naloxone can be given parenterally, 0.2–0.8 mg subcutaneously, or intramuscularly. It can also be used intravenously if very rapid results are desired.

When the naloxone challenge is negative, an injection of XR-NTX may be given or oral naltrexone can be started with an initial dose of 25 mg (one-half tablet). If no side effects occur within an hour, another 25 mg may be administered. The recommended dosage for oral naltrexone is 50 mg/day. It is critical that psychotherapy sessions be initiated early in treatment and that these sessions involve family members and other significant figures in the patient's life. Oral naltrexone ingestion should be observed, and patients receiving oral naltrexone should be carefully selected and closely monitored.

Adverse Effects of Naltrexone

Naltrexone has few side effects. Side effects reported include nausea, headache, and mild anxiety. Because naltrexone blocks endogenous opioid peptides in addition to injected opioid drugs, one would expect to find multiple symptoms related to blockage of the wide-ranging functions of the endorphin systems. However, most patients with former opioid dependence do not report subjective effects that can be related to naltrexone. In a study of patients given high-dose naltrexone for experimental treatment of obesity, there were increases in transaminase levels that were all reversible when the drug was stopped. These subjects received 300 mg/day of naltrexone, or about six times the therapeutic dosage for prevention of addiction relapse (Mitchell et al. 1987). Other studies of naltrexone for the treatment of addictions as well as other disorders showed no adverse effects on liver function (Croop et al. 1997; Marrazzi et al. 1997; Sax et al. 1994; Yen et al. 2006).

Individuals addicted to opioids who are in liver failure should not be given naltrexone, although those with minor abnormalities in liver function tests may receive naltrexone. Baseline laboratory tests must include a full battery of liver function studies, and retesting should occur periodically. Caution should be exercised in administering naltrexone to patients whose serum chemistry results (aspartate transaminase and alantine transaminase) are five times or more above normal.

Conclusion

Antagonists give clinicians more options in the treatment of opioid dependence. Although agonist treatments are safe and effective, some patients may not be able to tolerate methadone or buprenorphine or will simply prefer not to be treated with an agonist. Antagonists like naltrexone provide a safe and effective alternative that does not involve treatment with a controlled substance or treatment with a medication that provokes physical dependence. Antagonists have proven to be useful additions to the armamentarium of medications for the treatment of opioid dependence.

Recommended Readings

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CHAPTER 50

Opioid-Related Disorders: Agonist Maintenance Treatment

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Opioid use disorder is chronic and severe and is associated with substantial risk of mortality, morbidity, and adverse social, vocational, familial, and legal consequences. The goals of treatment are to prevent or reduce adverse consequences and to improve the patient's functioning and quality of life. Opioid agonist maintenance treatment generally refers to a comprehensive approach, including maintenance on an opioid agonist (in the United States, methadone or buprenorphine) in combination with drug counseling; behavioral monitoring; and provision of or referral to psychiatric, medical, or vocational services. Since its development in the 1960s, this approach has proven to be the most effective treatment for opioid dependence. Yet in the United States, of the estimated 1.7 million individuals meeting criteria for opioid use disorder (Substance Abuse and Mental Health Services Administration 2012), only 299,643 patients were treated with methadone maintenance (Substance Abuse and Mental Health Services Administration 2011). More than 650,000 patients were prescribed buprenorphine in the United States in 2009, but it is unclear how many were receiving maintenance treatment. Ensuring adequate funding and effectiveness of services and continuing to expand access through novel settings are critical for improving accessibility and availability of treatment.

Mortality and Natural History of Opioid Use Disorder

Opioid use disorder is associated with an increased risk of death (estimated 1%–2% risk of dying per year, mainly resulting from drug overdose, suicide, violence, accidents, or infection) and disability. In one study, nearly half of 581 men addicted to heroin had died within 33 years, only 23% were abstinent, and relapse was common even for those who had achieved sustained periods of abstinence (Hser et al. 2001). In young injection drug users, one study found a mortality rate of 9.1 per 1,000 person-years, 10 times that of the general population, with overdose (57.9%), self-inflicted injury (13.2%), trauma or accidents (10.5%), and injection drug user–related medical conditions (13.1%) as the leading causes of death (Evans et al. 2012).

Rationale for Opioid Agonist Maintenance Treatment

Opioid agonist maintenance treatment substitutes a less dangerous and less reinforcing route of administration (oral for methadone or sublingual for buprenorphine) for more dangerous and reinforcing routes (injection, smoking, intranasal). Daily dosing prevents withdrawal and craving and eliminates the repeated negative reinforcement that occurs when heroin or other illicit opioids are self-administered to relieve withdrawal. At sufficient doses, tolerance develops to the effects of street doses of heroin or other illicit opioids, thus attenuating their euphoric or rewarding effects. After stabilization on a maintenance dosage, the fluctuations in mood, alertness, or consciousness associated with use of short-acting opioids are minimized.

Effectiveness of Opioid Agonist Maintenance Treatment

Opioid agonist maintenance treatment substantially reduces illicit drug use (Hubbard et al. 2003). Mortality rates are also reduced substantially, although they remain somewhat higher than for the general population because of the impaired health of many patients at treatment entry (e.g., HIV infection or hepatitis C). HIV risk behaviors decrease during treatment, and the incidence of HIV infection is substantially reduced in patients maintained on methadone compared with untreated heroin users (MacArthur et al. 2012). Criminal activity decreases during treatment and has been found to increase substantially among individuals discharged from treatment because of the closing of public methadone programs after financial cutbacks (Anglin et al. 1989). Key components affecting agonist maintenance effectiveness include dosage, duration of treatment, counseling, and program structure (Faggiano et al. 2003; Mattick et al. 2008; Peles et al. 2011).

Clinical Pharmacology of Methadone and Buprenorphine

Methadone is a synthetic, long-acting, orally available opioid that acts primarily as a high-affinity agonist at μ and δ opiate receptors. Peak plasma levels occur 2–6 hours after oral administration, and the

long plasma half-life of methadone (averaging 24 hours, ranging from 13 to 50 hours) permits once-a-day dosing. Methadone accumulates in high concentrations in solid organs (liver, kidney, lungs, and brain). Methadone is metabolized primarily through the CYP3A4 and CYP2B6 pathways, but CYP2C19, CYP2C9, CYP2C8, and CYP2D6 are also involved. Trough concentrations exceeding 200 ng/mL are usually sufficient to prevent withdrawal, but withdrawal symptoms may also occur with rapid metabolism (Dyer et al. 1999).

Buprenorphine is a μ opioid receptor partial agonist and a κ opioid receptor antagonist that is highly protein bound and has a high μ opioid receptor affinity (Elkader and Sproule 2005; Lewis 1985; Rothman et al. 2000). Because it is a partial agonist, there is a "ceiling" to the effects from the activated μ opioid receptor. This provides some protection from respiratory depression and subsequent death that can occur in opioid overdose and attenuates euphoria compared with a full μ agonist (Wesson 2004). Because of its high affinity for the μ receptor, buprenorphine displaces opioids with lower affinity and may cause withdrawal symptoms in individuals physically dependent on opioids. Buprenorphine is administered for maintenance therapy as a sublingual formulation because of its poor oral bioavailability (about 29%) and extensive first-pass metabolism. The half-life of the sublingual formulation is about 37 hours, allowing for once daily or thrice weekly dosing. In the United States, buprenorphine is primarily administered in a combination sublingual film with naloxone. Naloxone has poor sublingual or oral bioavailability but is a potent opioid receptor antagonist by intravenous administration; it is added to the formulation to reduce diversion and injection abuse.

Advantages and Disadvantages of Agonist Maintenance Treatment

There are distinct advantages and disadvantages of methadone or buprenorphine. Factors that favor methadone include evidence for better retention in treatment and ease of induction (no risk of precipitated withdrawal) (Mattick et al. 2008). Factors that favor buprenorphine include the potential for treatment in a general office–based practice, fewer potential medication interactions, and less overdose risk in general and if diverted. Access to methadone can be a problem for many patients because of the limited number and locations of specialized opioid treatment facilities and the requirements for daily attendance for methadone dosing, at least prior to earning take-home dose privileges. Diversion can occur with both medications. Policies about methadone take-home dosages can reduce diversion. Buprenorphine diversion has increased in the United States since 2005, along with the expansion in the number of patients treated, but evidence suggests that most diverted buprenorphine in the United States is used to treat opioid withdrawal (Bazazi et al. 2011; MacArthur et al. 2012).

Safety, Toxicity, and Interactions With Other Systems

Methadone and buprenorphine have not been found to produce any long-term damage to heart, lung, kidney, liver, brain, or other organ systems, and maintenance leads to normalization of

most measures of endocrine and immune system functioning (Elkader and Sproule 2005; Kreek 2000); hypothalamic hypogonadism (with persistent depression of serum testosterone levels) is associated with long-term methadone treatment. The most frequent adverse effects of methadone and buprenorphine are similar to that of other opioids and can include constipation, sweating, urinary retention, and nausea. Methadone is also associated with cardiac conduction defects (prolonged QT interval) and torsade de pointes, most often with very high methadone doses used to treat chronic pain (Chugh et al. 2008).

Methadone can cause severe respiratory depression in individuals who are not tolerant of the methadone dose (Wolff 2002). Death has been reported to occur more than 24 hours after ingestion (and several hours after discontinuation of naloxone treatment for opioid overdose), pointing to the need for prolonged treatment of methadone overdose and close monitoring. Overdose deaths can occur at the onset of methadone maintenance treatment if induction onto methadone starts at too high a daily dose (in excess of 40–50 mg) or is increased too rapidly, especially in patients with diminished methadone metabolism from liver disease or concomitant medications. The partial agonist "ceiling effect" of buprenorphine makes it less likely to cause overdose, although concurrent alcohol or benzodiazepine use can lead to respiratory depression (Lintzeris and Nielsen 2010).

Agonist Induction, Dosage, and Treatment Duration

Effective methadone maintenance dosages generally fall within a targeted range of 60–120 mg/day (Faggiano et al. 2003), but actively using patients should be started at a lower daily dose (30–35 mg), and methadone doses should be increased gradually to the target maintenance dosage over a period of a few weeks in order to prevent overdose deaths during methadone induction. In experimental studies, daily doses of 30–60 mg are sufficient to suppress most withdrawal symptoms for 24–48 hours, but more complete attenuation of the effects of heroin occurs only with a higher daily dose of methadone (120 mg) (Donny et al. 2002). The optimal dose for a given patient, however, should be based on the patient's response to treatment because studies show wide variability of methadone plasma levels that do not always correspond to dose (Eap et al. 2000), and some patients may achieve stable abstinence at lower dosages. Several studies suggest that some poor responders to even relatively high methadone doses (e.g., 80–100 mg/day) have increased metabolism of methadone and respond better to even higher doses or twice daily dosing (Dyer et al. 1999).

Buprenorphine induction is usually accomplished over a period of 2–4 days. To reduce buprenorphine-induced precipitated withdrawal, patients should be opioid abstinent prior to starting the induction and should be experiencing mild opioid withdrawal. Patients who have been maintained on methadone should have the methadone tapered gradually to 30 mg or lower and then stopped for a day or two before transitioning to buprenorphine. Following a typical initial buprenorphine dose of 2–4 mg, additional doses of buprenorphine may be administered as tolerated every 4–6 hours during the first 2–3 days to reduce withdrawal. Insomnia, sweating, anxiety, and vomiting can occur (incidence >10%) during induction. Higher buprenorphine maintenance doses (16–24 mg daily) are

associated with better retention in treatment and greater reductions in illicit opioid use compared with lower daily maintenance doses (Fareed et al. 2012).

The risk of relapse following discontinuation of agonist maintenance remains high even for patients who have been maintained successfully for prolonged periods. Many patients may benefit optimally from lifetime maintenance; however, slow tapering of medications after stability has been achieved can be tried for patients who want to be medication-free.

Medication Interactions

Medications that induce specific cytochrome P450 hepatic isoenzymes increase methadone and buprenorphine metabolism, leading to reductions in plasma levels and possible opioid withdrawal in patients who have been maintained on methadone or buprenorphine (Iribarne et al. 1997; Rainey 2002). Medications that inhibit cytochrome P450 enzymes inhibit methadone and buprenorphine metabolism and may lead to sedation, confusion, or respiratory depression, especially during methadone induction (Iribarne et al. 1997). Discontinuation of medications inhibiting methadone metabolism can lead to increased methadone metabolism and withdrawal symptoms. Medication interactions with methadone and buprenorphine are not limited only to the cytochrome P450 system and can result from changes in gastrointestinal absorption and motility, plasma protein binding, or renal clearance or from effects on blood-brain transport mechanisms.

Methadone and buprenorphine interact with many medications. For example, methadone increases plasma levels and possibly dose-related toxicity of desipramine, amitriptyline, and zidovudine and may lead to increased duloxetine exposure (McCance-Katz et al. 2010b). St. John's wort can cause increased metabolism and elimination of buprenorphine (McCance-Katz et al. 2010b). Cocaine may cause increased metabolism and decreased plasma concentrations of buprenorphine (McCance-Katz et al. 2010a). Agonist interactions with antiretroviral medications are of particular interest because of the high prevalence of HIV infection among injection drug users (Rainey 2002). Interactions of benzodiazepines or alcohol with methadone or buprenorphine are of particular concern and can lead to sedation, confusion, respiratory depression, and death (White and Irvine 1999).

Table 50–1 shows some of the reported and possible medication interactions with methadone, as adapted from McCance-Katz et al. (2010b).

Agonist Treatment During Pregnancy

Opioid use disorder during pregnancy has adverse health effects on the pregnant woman, fetus, and neonate, resulting from a combination of chaotic lifestyle and poor self-care and nutrition, possible exposure to violence, direct drug effects, withdrawal, or infections associated with injection drug use and addiction (Archie 1998; Goel et al. 2011). Methadone or buprenorphine maintenance treatment coordinated with prenatal and obstetrical treatment and nutritional supplementation leads to substantial reductions in opioid use and improvements in nutrition, health status, and participation in prenatal care for pregnant women with opioid use disorders and also to improved fetal growth and perinatal outcomes in their offspring.

TABLE 50–1. Medication interactions

May reduce plasma methadone	May increase plasma methadone	Methadone may increase plasma levels	Methadone may decrease plasma levels
Carbamazepine	Amiodarone	Amitriptyline	Didanosine
Cocaine[a]	Amitriptyline	Desipramine	Stavudine
Darunavir	Cimetidine	Zidovudine	
Efavirenz	Ciprofloxacin		
Lopinavir/ritonavir	Clarithromycin		
Nelfinavir	Delavirdine		
Nevirapine	Erythromycin		
Phenytoin	Fluconazole		
Rifampin	Fluoxetine		
Risperidone	Fluvoxamine		
Ritonavir	Quetiapine		
St. John's wort	Saquinavir		
	Voriconazole		

[a]Trough levels.
Source. Adapted from McCance-Katz et al. 2010b.

Methadone maintenance is a well-supported option for treating opioid use disorders during pregnancy given the long-term experience with the medication and good maternal and neonatal outcomes, including higher birth weight compared with neonates born to mothers addicted to heroin (Jones et al. 2008; McCarthy et al. 2008). Because of the increased volume of distribution and metabolism of methadone during pregnancy, methadone dosages often need to be increased during the second and third trimesters to prevent withdrawal and to sustain treatment effectiveness. Splitting the daily methadone dose to twice-daily administration may reduce large fluctuations in methadone plasma levels and withdrawal symptoms resulting from increased methadone metabolism during pregnancy (Jansson et al. 2009).

One drawback of methadone maintenance during pregnancy is the occurrence of neonatal abstinence syndrome (NAS), experienced by 46%–81% of neonates, which may require medication management and prolonged hospitalization (2–3 weeks).

Recent studies also support buprenorphine maintenance treatment for pregnant women with opioid use disorders. Early treatment attrition may be greater for pregnant women inducted onto buprenorphine compared with methadone; however, there is less suppression of fetal cardiac and movement behaviors with buprenorphine as compared with methadone (Salisbury et al. 2012), and NAS may be less likely to occur or to require extended treatment or may be less severe (Jones et al. 2010).

Co-occurring Other Psychiatric or Substance Use Disorders

Co-occurring other psychiatric or substance use disorders are prevalent among individuals with opioid dependence entering agonist maintenance treatment and may affect prognosis (Craddock et al. 1997) and complicate treatment. Treatment of persistent depression, found in approximately 15%–25% of individuals entering treatment, may improve mood and reduce illicit drug use (Nunes et al. 1998). Because of the high risk of benzodiazepine abuse among individuals with opioid use disorders and potentially toxic interactions with opioid agonist medications, cognitive and behavioral treatments are the first-line treatments for sleep and anxiety disorders during opioid agonist maintenance treatment. Provision of psychiatric services along with maintenance treatment is effective, regardless of the severity of psychopathology, and with treatment, patients with co-occurring psychiatric disorders improve in terms of both substance use and psychiatric morbidity (Pani et al. 2011).

Co-occurring Medical Disorders and Provision of Medical Care

Because of drug and sexual risk behaviors, patients with opioid use disorders are at high risk for infectious diseases, including HIV (prevalence ranges from 3%–5% in cities in the Midwest and West to 29% in the Northeast), hepatitis B (prevalence 50%–80%) or hepatitis C (prevalence 66%–93%), and tuberculosis (Murrill et al. 2002). Opioid agonist maintenance therapy reduces HIV transmission risk. In a recent systemic review and meta-analysis, agonist maintenance treatment was associated with a 54% reduction in risk of HIV infection among people who inject drugs (MacArthur et al. 2012). Directly observed antiretroviral treatment during methadone dispensation results in improved adherence and appears to decrease development of resistance to antiretroviral medications (Brust et al. 2011).

The prevalence of many medical disorders common in the general population (e.g., hypertension, diabetes, heart or lung disease, or osteoporosis) is increased among patients maintained on opioid agonists. Given the increased prevalence of medical disorders in opioid agonist maintained patients, other preventive health services that could benefit patients during maintenance treatment include cigarette smoking cessation interventions; immunizations; promotion of exercise and good nutrition; and routine testing for HIV, hepatitis, other sexually transmitted diseases, and tuberculosis and treatment for those with evidence of infection or other medical disorders.

Pain Management During Opioid Agonist Maintenance Treatment

Pain management is complicated during agonist maintenance treatment by the development of tolerance to the analgesic effects of the maintenance dose, possible opioid-induced hyperalgesia (increased sensitivity to pain), and the high prevalence of co-occurring chronic pain among agonist-maintained patients. At treatment entry, about one-third of patients maintained on opioid agonists have severe chronic pain, and about 80% have some

pain. The pain is often associated with functional impairment (Rosenblum et al. 2003); more severe medical and psychological problems; and more severe misuse of opioid analgesics, sedatives, and marijuana than patients without pain (Trafton et al. 2004). When opioid analgesics are required to treat acute pain during maintenance treatment, patients may require higher than usual doses or more frequent administration of full opioid analgesic medications (Compton et al. 2012). Administration of a partial agonist (e.g., pentazocine, nalbuphine, butorphanol, or buprenorphine) may precipitate withdrawal in an agonist-maintained patient. The efficacy of opioid analgesic medications in treating patients maintained on buprenorphine may also be affected by the high binding affinity of buprenorphine; analgesia may be obtained by continuing buprenorphine and titrating a short-acting opioid analgesic to effect, administering buprenorphine in divided doses every 6 hours, or discontinuing buprenorphine and either using a short-acting opioid both to prevent withdrawal and to manage pain or substituting methadone for buprenorphine maintenance treatment and using additional opioid analgesics as needed to control pain (Alford et al. 2006).

Drug Counseling and Behavioral Components of Opioid Agonist Maintenance Treatment

Psychosocial interventions, including drug counseling, behavioral monitoring (e.g., urine toxicology testing), consistent response to the patient's behavior (e.g., increased frequency and intensity of required counseling for patients with continued illicit drug use), and positive reinforcement of abstinence and treatment participation (e.g., providing take-home methadone), may enhance the effectiveness of agonist maintenance treatment (Amato et al. 2011). Questions remain about whether all patients or specific subsets need or will benefit from additional interventions and about the optimal type, timing, and intensity of additional interventions. Some studies report no significant differences in treatment retention or illicit drug use at 12 months between interim methadone maintenance provided for the first 4 months (supervised methadone and no routine counseling), followed by standard methadone maintenance services for the remainder of the year, and standard services methadone maintenance from the outset of treatment (Schwartz et al. 2012).

Recent meta-analyses concluded that providing specific psychosocial interventions in addition to pharmacological treatment with methadone or buprenorphine compared with pharmacological treatment alone for detoxification reduces attrition from treatment, treatment interruptions, and illicit opioid use during treatment and at follow-up, although no single, specific approach was supported (Amato et al. 2004). Meta-analyses also indicated that there is insufficient evidence to conclude that adding specific psychosocial treatments to the standard services provided in methadone treatment programs is associated with additional benefit (Amato et al. 2011).

Federal Rules Governing Opioid Agonist Maintenance Treatment

Federal and state rules and guidelines regulate many aspects of opioid agonist maintenance treatment, including patient eligibility criteria, medications that can

be used for opioid agonist maintenance treatment, medication dispensing, and program guidelines. Eligibility for methadone maintenance treatment generally remains restricted to individuals age 18 years or older with at least a 1-year history of opioid use disorder, except for pregnant women, previously treated patients, or individuals following prison release. Persons younger than 18 years may be admitted to methadone maintenance if they have a history of repeated treatment failure (two or more documented attempts at short-term detoxification or drug-free treatment within past 12 months); parent or guardian consent is required for individuals younger than 18 years.

Buprenorphine is approved by the U.S. Food and Drug Administration for use in adolescents (generally age 16 and older) and adults. Longer-term buprenorphine treatment is associated with improved treatment retention and drug use outcomes for adolescents and young adults compared with short-term detoxification (Woody et al. 2008). There is also growing evidence for buprenorphine maintenance treatment with adolescents with a shorter duration of opioid use disorder or without prior treatment failures, especially considering the high risk of drug overdose in patients with opioid use disorders who are not receiving agonist maintenance treatment (Subramaniam et al. 2011; Warden et al. 2012).

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CHAPTER 51

Hallucinogen-Related Disorders

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The hallucinogens are a class of psychoactive drugs, either synthetic or plant products, that produce auditory and/or visual hallucinations as well as thought, mood, and perceptual changes. Depending on dosage, expectation (set), and environment (setting), they also can induce euphoria and a state similar to a transcendental experience. These hallucinations can be present as part of a delirium (e.g., from jimsonweed [*Datura stramonium*]) when accompanied by disturbances in judgment, orientation, intellect, memory, and emotion. Delirium also can result from drug withdrawal (e.g., associated with sedative-hypnotic and/or alcohol withdrawal).

When used in the context of substance abuse, the term *hallucinogen* generally refers to a compound that alters consciousness without producing delirium, sedation, excessive stimulation, or impairment of intellect or memory. Hallucinogens that are abused include the prototype hallucinogen *d*-lysergic acid diethylamide (LSD); other indolealkylamines such as psilocybin ("magic mushrooms") and dimethyltryptamine (DMT, also contained in the South American beverage ayahuasca); and the phenalkylamines, including mescaline and dimethoxymethylamphetamine (DOM, also called STP). LSD, DMT, DOM, psilocybin, and mescaline are sometimes characterized as *serotonergic hallucinogens* on account of their predominant effect on that receptor system. Other plant products with hallucinogenic activity that are abused include the

seeds of the morning glory (*Ipomoea*), which contain lysergic acid derivatives, and seeds of the Hawaiian baby woodrose (*Argyreia nervosa*), which contain lysergic acid amide. Cannabinoid agonists; κ agonists; antimuscarinic agents; dissociative anesthetics such as phencyclidine (PCP); and designer drugs such as methylenedioxymethamphetamine (MDMA or ecstasy), which are sometimes classified as hallucinogens, are covered elsewhere in this volume.

Physiological Effects of Hallucinogens

Serotonergic hallucinogens (e.g., LSD) produce significant sympathomimetic activity. They dilate the pupils, increase heart rate, and produce slight hypertension and hyperthermia. Piloerection, salivation, flushing, a fine tremor, and lacrimation and a minor degree of incoordination, restlessness, visual blurring, and a quickening of deep tendon reflexes can occur. DMT and ayahuasca (which contains DMT) also increase heart rate, pupil diameter, and body temperature, and DMT elevates plasma levels of corticotropin, cortisol, and prolactin (Riba et al. 2001; Strassman and Qualls 1994). These autonomic effects vary as a function of the anxiety state of the user. LSD also can cause nausea, and nausea and vomiting are especially noteworthy after the ingestion of mescaline.

LSD has a very high therapeutic index. The lethal dose in humans has not been determined, and fatalities that have been reported usually are secondary to accidental death, likely due to distortions of perception and judgment. Fatal overdose with the hallucinogens is rare, and case reports describe individuals surviving 10,000 μg of LSD, 100 times the average dose. Nevertheless, serious adverse effects have been reported, including hemiplegia (Sobel et al. 1971), a fibrotic inflammatory mass in the mesentery (Berk et al. 1999), and in one case of mushroom ingestion, multifocal cerebral demyelination (Spengos et al. 2000). Although mescaline is often viewed as posing a minimal health risk, a case of fatal peyote ingestion associated with Mallory-Weiss lacerations, probably as a result of peyote-induced vomiting, has been reported (Nolte and Zumwalt 1999). There is no evidence of brain cell damage, chromosomal abnormalities, or teratogenic effects after the use of the indole-type hallucinogens (i.e., LSD and psilocybin) or mescaline (e.g., Li and Lin 1998). Drug interactions involving the hallucinogens do not appear to be a common source of adverse reactions. In some reports, the effects of LSD were reduced after the chronic administration of monoamine oxidase inhibitors or selective serotonin reuptake inhibitor antidepressants, whereas the effects of LSD were increased after the chronic administration of lithium or tricyclic antidepressants (Bonson and Murphy 1996; Bonson et al. 1996; Resnick et al. 1964).

Psychological Effects of Hallucinogens

Although the general psychological effects are similar across different hallucinogenic agents, there is substantial variation related to contextual factors (set and setting) and physiological factors (rate of onset, duration of action, and absolute intensity of the effects). The absorption of LSD from the gastrointestinal tract and other mucous membranes occurs rapidly, with drug diffusion to all tissues, including the brain and across the placenta to

the fetus. The onset of psychological and behavioral effects occurs approximately 30–60 minutes after oral administration and peaks at 2–4 hours after administration, with a gradual dissipation of intoxication over 8–12 hours (Hofmann 1961). DMT produces similar effects but is inactive after oral administration and must be injected, sniffed, or smoked. It has a very rapid onset and short duration of action (60–120 minutes) (Strassman and Qualls 1994). The effects of psilocybin last about 2 hours (Vollenweider et al. 1998) and those of ayahuasca last approximately 4 hours (Riba et al. 2001). In contrast, the effects of DOM have been reported to last longer than 24 hours. LSD is one of the most potent hallucinogens known, with behavioral effects occurring in some individuals after doses as low as 20 μg. In the past, typical street doses ranged from 70 to 300 μg; however, some anecdotal evidence indicates that LSD on the streets today contains only 20–80 μg.

Hallucinogens produce profound perceptual alterations: colors are altered or intensified, visual patterns can form, afterimages can become prolonged, and fixed objects can undulate and flow. Frequently, users describe transcendent or mystical experiences, with perceptions of timelessness, ego dissolution, grandiosity, loosening of associations, and asyndesis. Auditory hallucinations seldom occur, but hyperacusis is common. Greater sensitivity to touch can be present, and sometimes taste and smell are altered. Synesthesia, an amalgamation of sensory experiences wherein colors are "heard" and sounds are "seen," is frequently described. The emotional responses to the hallucinogens can vary markedly. Initial apprehension or mild anxiety is common, but the most frequent response is one of euphoria, with accompanying elation and a "blissful calm." Less frequently, tension and anxiety culminating in panic can occur. Mood is labile, shifting readily between excitement and despair. Complete withdrawal (catatonic states) (Perera et al. 1995) and severe paranoid reactions have been observed. Although orientation typically remains intact, judgment may be impaired. Loosening of associations is regularly noted. Either a flight of ideas or a complete absence of thought can occur.

Diagnosis

Hallucinogen intoxication is a clinical diagnosis that can be established when the signs and symptoms described in Box 51–1 manifest in the context of recent hallucinogen ingestion (American Psychiatric Association 2013). Hallucinogen intoxication does not produce specific abnormalities in blood chemistries, blood counts, or urine analyses, and routine clinical drug screens usually do not include testing for hallucinogens in body fluids. However, hallucinogens can be detected in blood and plasma and for longer periods in urine by enzyme-linked immunosorbent assay, gas chromatography–mass spectrometry, or liquid chromatography–mass spectrometry. It should be noted that one immunoassay for LSD cross-reacted with the antidepressant sertraline (Citterio-Quentin et al. 2012).

Box 51–1. DSM-5 Diagnostic Criteria for Other Hallucinogen Intoxication

A. Recent use of a hallucinogen (other than phencyclidine).
B. Clinically significant problematic behavioral or psychological changes (e.g., marked anxiety or depression, ideas of reference, fear of "losing one's mind," paranoid ideation, impaired judgment) that developed during, or shortly after, hallucinogen use.

C. Perceptual changes occurring in a state of full wakefulness and alertness (e.g., subjective intensification of perceptions, depersonalization, derealization, illusions, hallucinations, synesthesias) that developed during, or shortly after, hallucinogen use.
D. Two (or more) of the following signs developing during, or shortly after, hallucinogen use:
   1. Pupillary dilation.
   2. Tachycardia.
   3. Sweating.
   4. Palpitations.
   5. Blurring of vision.
   6. Tremors.
   7. Incoordination.
E. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

Coding note: The ICD-9-CM code is **292.89.** The ICD-10-CM code depends on whether there is a comorbid hallucinogen use disorder. If a mild hallucinogen use disorder is comorbid, the ICD-10-CM code is **F16.129,** and if a moderate or severe hallucinogen use disorder is comorbid, the ICD-10-CM code is **F16.229.** If there is no comorbid hallucinogen use disorder, then the ICD-10-CM code is **F16.929.**

The differential diagnosis for hallucinogen intoxication also includes consumption of delirium-inducing drugs such as the atropine-like agents, PCP, or cannabis. Poisoning with compounds with atropine-like activity (e.g., jimsonweed) can be differentiated by the presence of prominent anticholinergic effects such as dry mouth and blurred vision. Cannabis-induced psychosis frequently occurs with drowsiness rather than with the hyperalertness characteristic of the LSD state. PCP psychosis is accompanied by marked neurological signs (e.g., vertical nystagmus and ataxia) and more pronounced autonomic effects than are seen with the hallucinogens. Individuals with psychostimulant-induced psychoses often fail to differentiate their perceptual distortions from reality, whereas LSD users are usually aware of the difference. The differential diagnosis also must distinguish intoxication from a hallucinogen-induced (or other drug-induced) psychosis. The differentiation is not always easily made. The use of hallucinogens may unmask vulnerabilities to psychosis as well as precipitate relapse among individuals with a preexisting psychotic disorder (Bowers 1987). Among individuals with schizophrenia, hallucinations are usually auditory, in contrast to the predominantly visual hallucinations from hallucinogens (Caton et al. 2005).

Treatment

Acute Adverse Reactions

The most common adverse effects from hallucinogens are acute dysphoric reactions, commonly known as "bad trips," characterized by anxiety, fear, depersonalization, and the perception of loss of control (Johnson et al. 2008). Less commonly, transient psychotic symptoms can occur, including thought disorder, paranoia, delusions, and hallucinations. Toxic delirium, characterized by confusion, inattentiveness, disorientation, waxing and

waning alertness, and agitation, has also been described. Such reactions typically resolve as intoxication dissipates, and supportive interventions, such as establishment of a safe environment and provision of reassurance, are useful. Prediction of who will have an adverse reaction is unreliable; a history of positive LSD experiences renders no immunity from an adverse reaction (Ungerleider et al. 1968). Individuals who place a premium on self-control, planning, and impulse control tend to be more susceptible. Traumatic and stressful external events can precipitate an adverse reaction. Although hallucinogenic effects tend to be proportional to dosage levels, adverse reactions have occurred after doses of LSD as low as 40 μg, whereas much higher doses (e.g., 2,000 μg) do not necessarily produce such effects. Thus, acute adverse reactions generally are not dose related but are a function of personal predisposition, set, and setting.

Treatment of acute adverse reactions first must be directed toward preventing patients from physically harming themselves or others. The "talk-down" technique, in which a clinician provides brief supportive interventions involving encouragement to stay calm, information about what is going on, and reassurance that symptoms are self-limited, is often effective. The provision of a safe, monitored environment is particularly critical because individuals suffering from hallucinogen-associated paranoia or grandiosity are at risk of engaging in self-destructive behavior. Because adverse reactions to hallucinogens can last from an hour to a few days, an extended period of unobtrusive protection and monitoring may be required.

Oral LSD is lipophilic and rapidly absorbed from the gastrointestinal system, such that administering activated charcoal or inducing vomiting with emetic agents is unlikely to be effective (Schwartz and Smith 1988). If medications are needed for persistent or severe anxiety, relatively short acting benzodiazepines such as lorazepam can be administered. Mildly agitated patients might accept oral administration of medications; however, it can be difficult to convince severely agitated and/or paranoid patients to swallow a pill, in which case parenteral administration might be necessary. Severely agitated or distressed patients who do not respond to a benzodiazepine can be given an antipsychotic agent. Caution must be used in administering antipsychotic drugs because they can lower the seizure threshold and elicit seizures, especially if the hallucinogen has been adulterated with contaminants that have convulsant activity, such as strychnine. Theoretically, selective serotonin type 2A receptor (5-HT_{2A}) antagonists should block many of the acute effects of hallucinogens; however, atypical antipsychotics with significant 5-HT_{2A} antagonist activity (e.g., clozapine, olanzapine, risperidone) also might be effective (Aghajanian 1994). Vollenweider et al. (1998) found that the psychotomimetic effects of psilocybin are blocked by the 5-HT_{2A} antagonists ketanserin and risperidone; however, haloperidol *increased* the psychotomimetic effects. It should be noted that there is some indication that risperidone might exacerbate flashbacks (Morehead 1997).

Chronic Adverse Reactions

Hallucinogen use does not commonly cause long-term neuropsychological disorders (Halpern and Pope 1999). Although patients usually recover from hallucinogen intoxication over several

hours to days, occasionally, symptoms of psychosis or delirium persist, and psychosis lasting from weeks to years has been described following hallucinogen use. Persistent symptoms should trigger an evaluation for longer-acting psychoactive substances as well as underlying psychiatric disorders (González-Maeso and Sealfon 2009). Although some evidence indicates that prolonged psychotic reactions tend to occur in individuals with poor premorbid adjustment, a history of psychiatric illness, and/or repeated use of hallucinogens, severe and prolonged illness has been reported in individuals without such a history (Strassman 1984). The pharmacological management of these prolonged psychotic reactions does not differ from that of other psychotic disorders (e.g., the use of antipsychotic drugs). The prognosis of these psychotic states is usually favorable; however, in a few patients, the psychotic reaction remains refractory to treatment.

In a few cases, anxiety and depression continue for unusually long periods following hallucinogen use. The use of LSD has been noted to coincide with the onset of depression, suggesting a possible role in the etiology of depression in young patients (Abraham and Fava 1999). A link between hallucinogen use and suicide attempts has also been reported, with one study suggesting a rate of completed suicides of 0.4–1.2 per 1,000 patients (Cohen 1960). However, more recent reviews of the literature suggest that although the risk of self-harm should not be minimized, a causal link is tenuous (Johnson et al. 2008). Treatment strategies for persisting mood and anxiety symptoms must extend beyond symptomatic management and should incorporate the possibility that hallucinogen intoxication activated unconscious psychological material, meriting supportive exploration and working through.

Hallucinogen Persisting Perception Disorder

A well-recognized adverse reaction unique to the hallucinogens and widely known as "the flashback" has been renamed *hallucinogen persisting perception disorder.* Clinically significant distress or impairment in functioning must be present to meet the diagnostic criteria (see Box 51–2), and it must be established that the individual is not currently intoxicated. Typical perceptual disturbances include "trailing images," images in the peripheral visual fields, afterimages, altered perceptions of real images (illusions) such as halos and enlarging (macropsia) or shrinking (micropsia) of surrounding objects, intensified colors, and geometric patterns (Halpern and Pope 2003). These effects are usually brief but can continue to recur spontaneously several weeks or months after the original drug exposure and can be precipitated by psychological stressors or use of other drugs. Because such persisting perceptions appear suddenly, unexpectedly, and inappropriately, they can generate significant distress. Only a small proportion of users of hallucinogens experience persisting perception disorder (Shick and Smith 1970). The phenomenon does not appear to be dose related and can develop after a single exposure to the drug (Levi and Miller 1990). Administration of selective serotonin reuptake inhibitor antidepressants (Markel et al. 1994) and risperidone (e.g., Lerner et al. 2002b) has been reported to initiate or exacerbate these recurrences in individuals with a history of LSD use.

The exact mechanism underlying hallucinogen persisting perception disorder remains obscure. It might represent a conditioned response learned during intoxication and triggered by subsequent states of hyperarousal (Cohen 1981). Alternatively, persisting changes in visual

processing might underlie these perceptions (e.g., Abraham and Duffy 2001). For example, prolonged afterimages (*palinopsia*) have been found in individuals several years after the last reported use of LSD (Kawasaki and Purvin 1996). A role for predisposing factors is suggested by the observation that individuals with hallucinogen persisting perception disorder have a high lifetime incidence of mood disorder compared with non-LSD-abusing substance abusers (Abraham and Aldridge 1994). Various pharmacological agents, such as α_2 agonists, benzodiazepines (Lerner et al. 2002a), or drug combinations (e.g., fluoxetine and olanzapine; Aldurra and Crayton 2001), are useful in the treatment of persisting perceptions, as is psychotherapy. The patient's physical and mental status should improve with these measures, and it is imperative that all substances with hallucinogenic activity, including cannabis, be avoided. Over time, persisting perceptions usually decrease in intensity, frequency, and duration, whether treated (i.e., with pharmacotherapy and/or reassurance) or not. If no recurrences have occurred during the 1–2 years since the last ingestion of the hallucinogen, it is unlikely that any more will occur.

Box 51–2. DSM-5 Diagnostic Criteria for Hallucinogen Persisting Perception Disorder

292.89 (F16.983)

A. Following cessation of use of a hallucinogen, the reexperiencing of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen (e.g., geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of color, intensified colors, trails of images of moving objects, positive afterimages, halos around objects, macropsia and micropsia).

B. The symptoms in Criterion A cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not attributable to another medical condition (e.g., anatomical lesions and infections of the brain, visual epilepsies) and are not better explained by another mental disorder (e.g., delirium, major neurocognitive disorder, schizophrenia) or hypnopompic hallucinations.

Other Hallucinogen Use Disorder

The term *hallucinogens* encompasses a wide range of substances with various physiological effects, reinforcing characteristics, behavioral patterns of use, and resulting disorders (Box 51–3). The serotonergic hallucinogens (LSD, psilocybin, DMT, DOM, and mescaline) are not associated with compulsive use because they are not classically reinforcing and they do not generate significant withdrawal symptoms. However, factor analyses over the past decade have demonstrated that hallucinogen use disorders can be reliably described, and, like other substance use disorders, they are best captured by a single diagnosis with a one-dimensional continuum of severity (Kerridge et al. 2011). Currently, the prevalence of hallucinogen use disorders continues a decades-long downward trajectory; the incidence of hallucinogen use disorders among individuals who have initiated use within the past 2 years is 2%–3% (Stone et al. 2006, 2007; Wu et al. 2010). A high degree of tolerance de-

velops to the behavioral effects of hallucinogens after repeated administration. Such behavioral tolerance develops very rapidly, after only several days of daily administration, and is lost rapidly after the individual stops taking the drug for several days. It should be pointed out that little tolerance develops to the various autonomic effects produced by the hallucinogens. Because of this rapid development of tolerance, hallucinogen use usually is limited to once or twice weekly and chronic daily use is exceedingly rare.

Box 51–3. DSM-5 Diagnostic Criteria for Other Hallucinogen Use Disorder

A. A problematic pattern of hallucinogen (other than phencyclidine) use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. The hallucinogen is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control hallucinogen use.
3. A great deal of time is spent in activities necessary to obtain the hallucinogen, use the hallucinogen, or recover from its effects.
4. Craving, or a strong desire or urge to use the hallucinogen.
5. Recurrent hallucinogen use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences from work or poor work performance related to hallucinogen use; hallucinogen-related absences, suspensions, or expulsions from school; neglect of children or household).
6. Continued hallucinogen use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the hallucinogen (e.g., arguments with a spouse about consequences of intoxication; physical fights).
7. Important social, occupational, or recreational activities are given up or reduced because of hallucinogen use.
8. Recurrent hallucinogen use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by the hallucinogen).
9. Hallucinogen use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the hallucinogen.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of the hallucinogen to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of the hallucinogen.

Note: Withdrawal symptoms and signs are not established for hallucinogens, and so this criterion does not apply.

Specify **the particular hallucinogen.**

Specify if:

In early remission: After full criteria for other hallucinogen use disorder were previously met, none of the criteria for other hallucinogen use disorder have been met for at least 3 months but for less than 12 months (with the exception that Criterion A4, "Craving, or a strong desire or urge to use the hallucinogen," may be met).

In sustained remission: After full criteria for other hallucinogen use disorder were previously met, none of the criteria for other hallucinogen use disorder have been met

at any time during a period of 12 months or longer (with the exception that Criterion A4, "Craving, or a strong desire or urge to use the hallucinogen," may be met).

Specify if:

In a controlled environment: This additional specifier is used if the individual is in an environment where access to hallucinogens is restricted.

Coding based on current severity: Note for ICD-10-CM codes: If a hallucinogen intoxication or another hallucinogen-induced mental disorder is also present, do not use the codes below for hallucinogen use disorder. Instead, the comorbid hallucinogen use disorder is indicated in the 4th character of the hallucinogen-induced disorder code (see the coding note for hallucinogen intoxication or specific hallucinogen-induced mental disorder). For example, if there is comorbid hallucinogen-induced psychotic disorder and hallucinogen use disorder, only the hallucinogen-induced psychotic disorder code is given, with the 4th character indicating whether the comorbid hallucinogen use disorder is mild, moderate, or severe: F16.159 for mild hallucinogen use disorder with hallucinogen-induced psychotic disorder or F16.259 for a moderate or severe hallucinogen use disorder with hallucinogen-induced psychotic disorder.

Specify current severity:

305.30 (F16.10) Mild: Presence of 2–3 symptoms.

304.50 (F16.20) Moderate: Presence of 4–5 symptoms.

304.50 (F16.20) Severe: Presence of 6 or more symptoms.

The literature on targeted treatments for hallucinogen use disorder is sparse. No medication has been shown to be effective in treating hallucinogen use disorder, and no manualized therapy has been studied. Patients with hallucinogen use disorder should be counseled to abstain from all recreational substances, and clinicians can utilize standard evidence-based psychotherapies for substance use disorders, such as motivational interviewing, supportive psychotherapy, contingency management, relapse prevention, and 12-step facilitation (detailed in Chapter 46, "Alcohol-Related Disorders"). Among at-risk populations, education on the risks of hallucinogens should be undertaken, particularly given the propensity for accidental injuries to occur in environments where misjudgments can have severe consequences. Clinicians should also be aware of the risk of hallucinogens being adulterated and the fact that in the age of e-commerce, individuals have access to a far wider array of hallucinogenic substances than was previously available.

Conclusion

The hallucinogens are a class of psychoactive drugs, either synthetic or plant products, that produce auditory and/or visual hallucinations as well as thought, mood, and perceptual changes. Focusing on the prototype hallucinogen LSD, the physiological and psychological effects have been described along with differential diagnosis of hallucinogen intoxication. Although there are strategies for the treatment of acute and chronic adverse reactions, there is no specific pharmacological or psychotherapeutic treatment for hallucinogen use disorder. To date, the best approach is to use evidence-based psychotherapies shown to be effective for other substance use disorders.

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CHAPTER 52

Cannabis-Related Disorders

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Marijuana is the most commonly used illicit substance in the United States and worldwide, and 1 in 11 individuals exposed to marijuana develops cannabis use disorder (Swift et al. 2001; United Nations Office on Drugs and Crime 2011). Despite public perception of marijuana as a generally benign substance, its addictive properties and associated adverse effects have been well documented (Hall and Degenhardt 2009). Of particular concern, adolescents and young adults are especially prone to developing cannabis-related disorders, and marijuana is the most common primary substance of use among people presenting for substance-related treatment (Chen and Anthony 2003; Substance Abuse and Mental Health Association 2010). Despite this, treatment development for cannabis-related disorders has lagged behind similar lines of development targeting other substance use disorders. Psychosocial interventions hold the strongest evidence base at present, but limitations in abstinence outcomes have led to investigation of more intensive psychosocial strategies, combined psychotherapeutic approaches, and augmentation of psychotherapy with pharmacotherapy.

Psychotherapeutic Approaches

Psychotherapeutic approaches have been the most extensively studied of approaches for the treatment of cannabis dependence. Although there has been early work using controversial aversive approaches such as emetic agents and electric shock (Morakinyo 1983; Smith et al. 1988), similar to alcohol and other drugs of abuse, the most commonly utilized approaches have been motivational interviewing, 12-step facilitation coun-

seling, cognitive-behavioral therapy, and contingency management strategies.

Comparisons of Various Psychotherapies

Adult Studies

Several questions arise when treating individuals with cannabis use disorders. Specifically, is one form of treatment better than another type, is more treatment preferable to less treatment, and does the effect of treatment maintain itself after the formal treatment has ended? Various studies have helped elucidate these questions. An uncontrolled trial of 33 adult marijuana users examined an integrated brief intervention for cannabis use disorder consisting of a two-and-a-half-hour assessment and intervention that provided education and use reduction strategies along with a self-help booklet (Lang et al. 2000). At follow-up, the investigators found that the mean number of days using, amount of marijuana use, and marijuana-related problems had decreased, although it was not reported if these changes were significant.

In a single-site study with 212 treatment-seeking marijuana users, Stephens and colleagues (1994) found that 10 group sessions of relapse prevention therapy or social support therapy produced significant reductions in frequency and amount of marijuana use, but neither group was superior in terms of treatment response. In a subsequent trial, Stephens and colleagues (2000) assessed brief versus extended treatment approaches. Two hundred ninety-one adult marijuana users seeking treatment were randomly assigned to participate in two sessions of individual motivational enhancement and cognitive-behavioral techniques, 14 sessions of a relapse prevention and social support group, or a delayed-treatment control group. Both treatment groups had a reduction in the frequency and amount of use at the end of treatment. At follow-up, as in the earlier study, there were no group differences in the active treatment arms.

Another study evaluating the impact of treatment length (while keeping the type of treatment constant) randomly assigned 229 marijuana treatment seekers to a single session of cognitive-behavioral therapy (CBT), six sessions of CBT, or a delayed control group (Copeland et al. 2001). Again, both treatment groups had significantly more reported days of abstinence, but there were no treatment group differences.

Combined, these data would suggest that no type of treatment or length of treatment is superior to another. However, a recent large trial suggests that a lengthier combined therapy may produce better results than fewer therapy sessions of a single approach. Specifically, in a large multisite trial consisting of 450 adults with cannabis dependence, participants were randomly assigned to three treatment arms: 1) two sessions of motivational enhancement therapy (MET), 2) nine sessions of MET with CBT and case management, and 3) delayed-treatment control (Marijuana Treatment Project Research Group 2004). Again, both active treatment groups had similar improvement and produced superior results compared with the control group during the trial. However, 4 months after randomization, the combined treatment group was more likely to be abstinent for 90 days (22.6%) compared with the two-session MET group (8.6%) or the delayed-treatment control group (3.6%).

Contingency management strategies, commonly tested in cocaine users, have been increasingly investigated in groups with cannabis use disorder. Budney and colleagues (2000, 2006) have conducted

two studies demonstrating the utility of voucher incentives in promoting marijuana abstinence. In one study, 60 marijuana users were randomly assigned to motivational enhancement, motivational enhancement plus behavioral coping skills therapy (MBT), or MBT plus voucher-based incentives (MBTV). MBTV outperformed the other two treatment groups in terms of duration of continuous abstinence and end-of-treatment abstinence. In a 14-week study, investigators randomly assigned 90 treatment-seeking adult marijuana users to abstinence-based vouchers alone (participants received vouchers with monetary value for each marijuana-negative urine sample), CBT alone with vouchers given regardless of whether urine samples were positive or negative, or combined CBT and voucher incentives (Budney et al. 2006). During the active treatment study, the voucher group had a significantly greater mean weeks of continuous abstinence compared with the CBT group. Although the voucher-alone group had greater mean weeks of abstinence than the combined CBT and voucher group, the difference was not significant. Notably, 3 months poststudy, the percentage of individuals abstinent in the combined group (43%) was substantially higher than the percentage of individuals abstinent in the voucher or CBT alone groups (17% and 20%, respectively).

Another study also employing contingency management techniques randomly assigned 240 adults with cannabis dependence to contingency management alone, individual MET and CBT with contingency management, or a case management control condition. The two contingency management groups had superior abstinence rates (Kadden et al. 2007). Similar to the earlier study, the contingency management alone group outperformed the other two groups at the end of treatment. However, at later follow-ups, the group that employed additional psychotherapies (MET/CBT) had the highest rate of abstinence. Similarly, in a recent randomized study with primarily young males ($N=127$) referred from the criminal justice system, the group receiving a combination of CBT and contingency management had lower rates of abstinence during and after treatment than those assigned to receive CBT alone or contingency management alone (Carroll et al. 2012). The authors noted that the high dropout and higher rates of antisocial personality disorder in the combined treatment group may have confounded the results.

Other approaches that are currently being evaluated include implementation of aerobic exercise and computer delivery of commonly used therapies. Buchowski and colleagues (2011) in a small nonrandomized trial of adult marijuana users found that there was a reduction in marijuana use during a 2-week regimen of daily 30-minute exercise sessions on a treadmill. Budney and colleagues (2011) in a nonrandomized treatment trial compared in-person versus computerized delivery of MET/CBT with contingency management. Because there was no difference between the groups in reduction in use, this suggests that computerized treatment may be a cost-effective and feasible approach worthy of further study.

Adolescent Studies

In a randomized controlled trial with 310 adolescent marijuana users, brief MET was compared with an educational feedback control or a delayed-treatment control (Walker et al. 2011). Both treatment groups had greater reduction in use and negative consequences than the delayed-treatment control group at follow-up.

The MET group had greater reduction in use but not greater reduction in negative consequences compared with the educational feedback control group. Following the completion of treatment sessions, all participants were offered optional individual treatment sessions aimed at cessation of marijuana use, but few engaged in additional treatment.

The largest psychotherapy trial to date is the Cannabis Youth Treatment Study, which assessed five treatment protocols of differing types and intensity, lasting 6–14 weeks (Dennis et al. 2004). Each therapy was recommended by an expert panel or determined through review of the treatment literature. Six hundred adolescent marijuana users were randomly assigned to receive one of five treatments: 1) five sessions that included two MET and three CBT sessions; 2) twelve sessions that included two MET and ten CBT sessions (MET/CBT12); 3) family support network, a multicomponent treatment designed to be added to MET/CBT12; 4) the adolescent community reinforcement approach, which is composed of 10 individual sessions and four sessions with the caregivers to educate them how to support the adolescent's abstinence; and 5) twelve sessions of a multidimensional family therapy, which is a family-focused therapy designed to work individually with adolescents and their families (Dennis et al. 2002; Diamond et al. 2002). Two separate clinical trials were carried out. One compared treatment arms with increased length of treatment and additional family involvement. The other trial varied both the type and the length of treatment. Individuals were repeatedly assessed over a 1-year follow-up period. No treatment approach was found to be superior in terms of days of abstinence or dependence problems between randomization and at the 12-month follow-up. Overall, the percentage of no use in the past month increased from 4% at baseline to 34% at end of treatment. Similarly, days of use were reduced by 36% from baseline to end of treatment.

Another recent randomized trial conducted in the Netherlands compared multidimensional family therapy and CBT in 109 adolescent marijuana users. As in the Cannabis Youth Treatment Study, the investigators found that both groups had a reduction in use but that neither was superior (Hendriks et al. 2011).

Contingency management has also been evaluated and compared with other approaches in adolescent and young adult populations. Carroll and colleagues (2006) compared the use of contingency management with MET/CBT, contingency management with individual drug counseling, MET/CBT with skills building, and individual drug counseling alone in youths referred by the criminal justice system. Again, there was a significant main effect of contingency management. The combination of MET/CBT plus contingency management was more effective than MET/CBT with skills building or contingency management with drug counseling. Both of the later approaches were more effective than drug counseling alone. Participants receiving contingency management or individual drug counseling alone had an increase in frequency of marijuana use poststudy, whereas participants receiving MET/CBT (with or without contingency management) demonstrated a reduction in marijuana use. In a subsequent study, Stanger and colleagues (2009) evaluated 69 adolescent marijuana users randomly assigned either to an experimental group (individualized MET/CBT, abstinence-based incentive program, parental monitoring, and drug testing) or to a control group (individualized MET/CBT, parental monitoring, and drug testing). The ex-

perimental group had greater mean weeks of continuous abstinence compared with the control group (7.6 weeks vs. 5.1 weeks). However, there were no substantive differences between groups at follow-up. After the formal treatment ended, there was some worsening of drug use, but the increased use leveled off and remained less than use at baseline.

Summary of Psychotherapeutic Approaches

Taken together, the studies show that there are ample data to suggest that various psychotherapeutic approaches are effective in reducing marijuana use. Contingency management strategies appear to be more effective in promoting abstinence than other behavioral interventions, but this superiority may not be maintained after active treatment has ended in most patient populations unless CBT is added during treatment. One criticism of voucher incentives is that they cannot be easily implemented in community treatment settings. However, prize-based contingency methods may be more cost-effective than vouchers and have been utilized with good effect (Olmstead and Petry 2009; Petry et al. 2007). These methods, along with other practical strategies, might allow the translation and implementation of incentivized approaches into community treatment settings.

Pharmacotherapeutic Approaches

Although psychosocial interventions remain the mainstay of treatment for cannabis use disorders, several factors suggest that development of pharmacotherapies is indicated. Amid increasing rates of marijuana use and increasing potency of marijuana, the prevalence of cannabis-related disorders is likely to remain high. Most psychosocial interventions convey only small to modest effect sizes, and few patients achieve and sustain abstinence, even when receiving evidence-based care. Increased understanding of the neuropharmacology of marijuana use, and neurotransmitter pathways in general, allows for informed identification and evaluation of promising candidate pharmacotherapies.

As indicated by established pharmacotherapies for other substance use disorders, a number of potential roles for medication treatment may be considered. First, medications may be used to target substance craving and withdrawal symptoms (e.g., varenicline in nicotine dependence). Second, medications may be used to block the reinforcing effects of the substance (e.g., naltrexone in opioid dependence). Third, medications may produce negative or aversive effects when the substance is used (e.g., disulfiram in alcohol dependence). Fourth, medications may act as a safer long-term alternative or substitution agent for the substance (e.g., methadone in opioid dependence).

Human Laboratory Studies

The cannabis withdrawal syndrome has been well described and, while nonfatal, may be markedly unpleasant and is considered a significant barrier to cessation. A number of human laboratory studies have investigated candidate pharmacotherapies targeting cannabis withdrawal, including divalproex (Haney et al. 2004), lithium (Winstock et al. 2009), sustained-release bupropion (Haney et al. 2001), nefazodone (Haney et al. 2003b), baclofen (Haney et al. 2010), mirtazapine (Haney

et al. 2010), oral tetrahydrocannabinol (Budney et al. 2007; Haney et al. 2004), combined lofexidine and oral tetrahydrocannabinol (Haney et al. 2008), and extended-release zolpidem (Vandrey et al. 2011). Among these, the most promising in laboratory conditions were oral tetrahydrocannabinol, combined lofexidine and oral tetrahydrocannabinol, and extended-release zolpidem. Oral tetrahydrocannabinol reduced marijuana craving and withdrawal symptoms, while combined lofexidine and oral tetrahydrocannabinol was superior to either intervention alone, ameliorating cessation-associated sleep disturbance, craving, and overall withdrawal symptoms while also reducing relapse in the laboratory model. Extended-release zolpidem restored abstinence-associated sleep architecture and sleep efficiency disturbances but did not reduce sleep latency.

On the basis of animal studies suggesting that the opioid antagonist naltrexone may reduce reinforcing effects of marijuana use and thus play a potential role in treatment, human laboratory trials were conducted. Findings demonstrated that in humans, naltrexone instead acutely *enhances* subjective effects of marijuana use among heavy users (Cooper and Haney 2010; Haney et al. 2003a; Wachtel and de Wit 2000). A more successful laboratory-administered medication in this vein is the cannabinoid receptor reverse agonist rimonabant, which blocks subjective effects of smoked marijuana (Huestis et al. 2001, 2007). Although this finding stimulated significant interest in further clinical testing, rimonabant was not granted U.S. Food and Drug Administration approval because of psychiatric safety concerns.

Clinical Trials

After an initial proof-of-concept placebo-controlled pilot trial of divalproex (Levin et al. 2004), a small but increasing number of controlled clinical trials evaluating candidate medications for cannabis use disorder have been conducted. Although trials of sustained-release bupropion, nefazodone, and atomoxetine had generally discouraging results (Carpenter et al. 2009; McRae-Clark et al. 2010; Tirado et al. 2008), other trials have been more promising.

In a 12-week preliminary controlled trial ($N=50$) of buspirone (maximum dose 60 mg/day) added to motivational interviewing, study completers in the buspirone group achieved a higher percentage of negative urine cannabinoid tests than those in the placebo group (McRae-Clark et al. 2009). In the modified intent-to-treat analysis (including all randomly assigned participants who submitted at least one urine cannabinoid test sample after starting study medication), the model-based estimate of proportion of negative urine cannabinoid tests was 28.8% in the buspirone group and 11.0% in the placebo group. This finding was only at a trend level, potentially owing to the small sample size. A subsequent fully powered buspirone trial is currently ongoing.

A 12-week controlled trial ($N=50$) of gabapentin (1,200 mg/day) added to weekly abstinence-oriented individual counseling revealed reduced marijuana use (measured by self-report and by quantitative urine cannabinoid testing), decreased cannabis withdrawal symptoms, and improved cognitive performance in gabapentin-treated participants relative to placebo participants (Mason et al. 2012). Although there were no reported significant between-group differences in cessation outcomes in this preliminary trial, the authors are currently conducting a subsequent fully powered flexible dose study of gabapentin.

Oral tetrahydrocannabinol (20 mg twice daily) added to motivational inter-

viewing and relapse prevention interventions was evaluated as an agonist substitution therapy in a 12-week controlled trial (N=156) (Levin et al. 2011). Although participants in the oral tetrahydrocannabinol group tolerated the medication well, were more likely than placebo participants to complete the trial (77% versus 61% of participants completed the trial, respectively), and experienced less severe withdrawal symptoms than placebo participants, there were no significant between-group differences in cessation outcomes. In the last 2 weeks of treatment, 17.7% of oral tetrahydrocannabinol participants and 15.6% of placebo participants were abstinent. The authors suggest that future research may explore higher doses of oral tetrahydrocannabinol and/or incorporation of more aggressive psychosocial treatments. Given the aforementioned encouraging human laboratory findings with combined lofexidine and oral tetrahydrocannabinol, an ongoing controlled trial is being conducted to evaluate whether this combination may yield significant abstinence outcomes.

An 8-week controlled trial (N=116) of *N*-acetylcysteine (1,200 mg twice daily) added to weekly cessation counseling and a contingency management intervention was conducted in adolescents with cannabis use disorder (Gray et al. 2012). Results indicated that participants receiving *N*-acetylcysteine had more than twice the odds of submitting negative urine cannabinoid tests than placebo participants. Overall, 40.9% and 27.2% of weekly urine cannabinoid tests were negative during treatment in the *N*-acetylcysteine and placebo groups, respectively. During the last 2 weeks of treatment, 36.2% of *N*-acetylcysteine participants were abstinent, compared with 20.7% of placebo participants. Work is under way to evaluate this intervention with adults with cannabis use disorder, and future trials may evaluate whether dosing adjustment or combination with different psychosocial interventions may convey differential efficacy.

Summary of Pharmacotherapeutic Approaches

Development of medications for the treatment of cannabis use disorder remains in the early stages but has progressed significantly in the last decade. Several laboratory studies have helped screen promising agents targeting withdrawal and relapse, and a handful of placebo-controlled clinical trials have evaluated medications to complement psychosocial treatments in real-world conditions. Among these, the only medication with a significantly superior intent-to-treat primary cessation outcome is *N*-acetylcysteine. Preliminary findings with buspirone and gabapentin are also encouraging, and combination treatments, such as dronabinol and lofexidine, may hold promise as well. Current and future research with these and other medications may broaden the array of available pharmacotherapies targeting cannabis use disorder. Further work is also needed to clarify the optimal combination of psychosocial and pharmacological interventions to maximize treatment outcomes.

Conclusion

Marijuana use is prevalent, and a significant proportion of users develop symptoms consistent with cannabis-related disorders. Many of these individuals seek treatment, and clinicians should provide them with evidence-based in-

terventions. The bulk of evidence supports psychosocial interventions, and a number of modalities appear effective. Among these, contingency management appears particularly effective in the establishment of marijuana abstinence, and combining contingency management with other treatments, such as cognitive-behavioral therapy, may help sustain treatment response. In contrast to psychosocial treatments, only a small number of pharmacological treatments have been investigated on a sufficient scale to infer conclusions about efficacy. To date, *N*-acetylcysteine possesses the strongest evidence. Other potentially promising agents, including buspirone, gabapentin, and the combination of lofexidine and oral tetrahydrocannabinol, are the subjects of ongoing investigation. However, at this stage, medication treatment should be considered only as a potential complement to evidence-based psychosocial treatment.

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CHAPTER 53

Club Drug Addiction

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Club drugs are licit and illicit drugs from different classes used primarily by young adults in bars, clubs, concerts, and dance parties or "raves." The National Institute on Drug Abuse (NIDA) has identified six substances as club drugs: ketamine, methylenedioxymethamphetamine (MDMA), methamphetamine, gamma-hydroxybutyrate (GHB), flunitrazepam, and lysergic acid diethylamide (LSD). Other drugs used in the club drug scene include phencyclidine (PCP), prescription opioids and benzodiazepines, and such over-the-counter drugs as dextromethorphan and pseudoephedrine (Weaver 2012a) (see Table 53–1). There is wide geographic variation in the popularity of different club drugs, and the scene changes rapidly. Club drugs are used because of the perception that they enhance the sensory experience at dance parties where strobe lights, glow sticks, and "techno" music (i.e., wordless music with a driving beat) are part of the overall event (Weaver and Schnoll 2008).

According to the 2010 National Survey on Drug Use and Health, the prevalence of past month "hallucinogen" use (also known as current use and including phencyclidine and MDMA) was 0.5% among persons age 12 or older (see also Chapter 51, "Hallucinogen-Related Disorders," in this volume). The number of persons age 12 or older who were current users of methamphetamine in 2010 was 353,000, or 0.1% of the U.S. population. The numbers and percentages for current users of MDMA were 695,000 (0.3%) in 2010 and 760,000 (0.3%) in 2009 (Merikangas and McClair 2012). The epidemiology of other club drugs, such as ketamine, methamphetamine, GHB, and flunitrazepam, is not captured in national surveys.

Acute Intoxication

Urine or serum toxicology screens may not be able to detect all club drugs. Patients may present with concurrent inges-

TABLE 53–1. Club drugs

Drug class	Chemical name	Abbreviation	Brand name	Slang names
Dissociative	Ketamine		Ketalar	Special K, kit cat, cat valium
	Phencyclidine	PCP		Angel dust, PeaCe pill
Stimulant	Methamphetamine		Desoxyn	Crank, crystal meth, ice, speed
	Methylenedioxy-methamphetamine	MDMA		Ecstasy, X, Adam
Sedative	Gamma-hydroxy-butyrate	GHB	Xyrem	Georgia home boy, Grievous bodily harm, liquid ecstasy
	Flunitrazepam		Rohypnol	Roofies, rope, Mexican Valium

tion of drugs with different pharmacological profiles, including both stimulant and depressant drugs. Internet Web sites may be helpful for identification of specific substances ingested because of their rapidly changing appearance (Gahlinger 2004). The lack of research-based information on adverse effects of club drugs has led to the emergence of a range of Web sites that may or may not provide accurate information (Chakraborty et al. 2011).

Ketamine and Phencyclidine

Ketamine and phencyclidine are dissociative anesthetics that produce perceptual distortions similar to hallucinogens as well as other effects. Ketamine is a derivative of phencyclidine that is less potent and shorter acting, and it is still used therapeutically in medical settings as an anesthetic in humans. Phencyclidine produces brief dissociative psychotic reactions similar to schizophrenic psychoses; these reactions are characterized by changes in body image (feeling that the body is made of wood, plastic, or rubber) and possible feelings of spiritual separation from the body. Ketamine effects include profound changes in consciousness and psychotomimetic effects similar to those of phencyclidine, including out-of-body experiences.

Several clinical trials have evaluated ketamine as a treatment for major depression that has been resistant to other medications and electroconvulsive therapy and for depression associated with bipolar disorder (Aan Het Rot et al. 2012). All trials have involved a single dose of ketamine given as an intravenous infusion in a hospital setting with monitoring for 24 hours after. Response has been rapid, with rates of improvement ranging from 25% to 85% at 24 hours and 14% to 70% at 72 hours after the infusion. Side effects have been mild and research is ongoing, although ketamine administration is not recommended outside of a hospital setting for treatment of refractory depression.

A "bad trip" is a feeling of extreme anxiety that may occur during a period

of drug effects ("trip") from hallucinogens or dissociatives such as ketamine or phencyclidine. A bad trip can be caused by fear, anxiety, or anger at the time the drug is taken; it may be difficult to distinguish between a bad trip and an acute psychotic reaction. Most bad trips can be handled without medication. It is important to make physical contact with the patient (e.g., holding hands) when treating a bad trip; this may be the only means of contact with someone who is having very severe hallucinations. Try to make contact with the patient during lucid intervals and maintain this contact into the intense periods of the drug's effects; attempting to make contact with the patient during intense drug effect is generally unsuccessful. The patient may react suddenly or violently to a touch. The physical space in which treatment takes place should be quiet, softly lit, and away from large groups of people. Excessive stimuli may overwhelm the patient; absence of stimuli, however, may intensify the hallucinations. Severe agitation may be treated with a benzodiazepine or haloperidol.

Ketamine can induce a state of virtual helplessness and pronounced lack of coordination. This is known to users as "being in a K-hole" and can be problematic if the user is in a public setting (Jansen 1993).

Acute physiological complications of ketamine or phencyclidine intoxication rarely require medical treatment. However, malignant hyperthermia and seizures may occur. Agitation, dry skin, and increased muscle tension are warning signs for hyperthermia, which may occur many hours after use. Rapid cooling measures (e.g., ice packs, cooling blanket) may be required (Weaver 2012b).

Phencyclidine can be taken orally, intranasally insufflated, smoked, or injected, and the half-life has been reported to vary from 7 to 46 hours. Both phencyclidine and ketamine are antagonists at the *N*-methyl-D-aspartate (NMDA) receptor (Anis et al. 1983), which enhances glutamate release and leads to neuronal excitation and blocks inhibition by γ-aminobutyric acid (GABA) neurons (Drejer and Honoré 1987). In high doses, phencyclidine produces seizures and severe hypertension. Intravenous antihypertensive medications should be administered to reduce blood pressure. The hypertension should be treated vigorously because it may cause hypertensive encephalopathy or intracerebral bleeding. A dissociative phenomenon occurs occasionally, with phencyclidine abusers exhibiting dangerous or violent behaviors (Marrs-Simon et al. 1988). Levels of consciousness may fluctuate rapidly while the patient is recovering from the intoxication. If the patient is severely agitated or psychotic and poses a potential threat to self or others, haloperidol or lorazepam is effective to control agitation; barbiturates may be even more efficacious (Olney et al. 1991).

Methamphetamine and MDMA

Methamphetamine is a stimulant that is classified as a club drug by NIDA. Methylenedioxymethamphetamine (MDMA, ecstasy) is a designer drug that is also a stimulant but has hallucinogen-like effects. It affects monoamine transporters, causing enhanced release of serotonin, dopamine, and norepinephrine into the synaptic cleft (Capela et al. 2009). Stimulants are typically taken as tablets when used as club drugs but can be intranasally insufflated (sniffed, snorted) or smoked.

The short-term complications of stimulants are due to increased sympathomimetic effects. The acutely intoxicated stimulant user should be approached in

a subdued manner; the person approaching should never speak in a loud voice or move quickly and never approach the patient from behind, and should try to avoid touching the patient unless absolutely sure it is safe to do so (Weaver and Schnoll 1999). Treatment for acute toxicity includes acute stabilization of airway, breathing, and circulation; use of activated charcoal; seizure control with benzodiazepines; aggressive management of hypertension with α and β antagonists or vasodilators; management of hyperthermia; and consideration of urine acidification (Weaver 2010). Other serious consequences of MDMA use include hyponatremia and rhabdomyolysis (Ricaurte and McCann 2005). Some serotonin reuptake inhibitor antidepressants may protect against MDMA-induced serotonergic toxicity (El-Mallakh and Abraham 2007).

Gamma-Hydroxybutyrate

Gamma-hydroxybutyrate is a sedative that is both a precursor and a metabolite of GABA. It has been used as a sleep aid as well as for treatment of narcolepsy (Lammers et al. 1993). It also increases episodic secretion of growth hormone, so some bodybuilders use it to promote muscle growth. Its effects have been likened to those of alcohol, another GABA-like drug (McCabe et al. 1971). As little as double the euphorigenic dose of GHB may cause serious central nervous system depression. GHB has synergistic effects with alcohol and other sedatives, so concurrent use may increase the risk of overdose. Use of GHB and stimulants may increase the risk of seizure.

In cases of acute GHB intoxication, medical personnel should provide physiological support and maintain a high index of suspicion for intoxication with other drugs. Most patients who overdose on GHB recover completely if they receive proper medical attention. Management of GHB ingestion in a spontaneously breathing patient (Li et al. 1998) includes oxygen supplementation, intravenous access, and comprehensive physiological and cardiac monitoring. Medical staff should attempt to keep the patient stimulated; atropine is used for persistent symptomatic bradycardia. The patient should be admitted to the hospital if he or she is still intoxicated after 6 hours; patients whose breathing is labored should be managed in the intensive care unit. If a patient is clinically well in 6 hours, then he or she can be discharged with plans for follow-up.

Flunitrazepam

Flunitrazepam is a short-acting benzodiazepine that is available by prescription in South America and Europe but not in the United States. Its potency is about 10 times that of diazepam (Gahlinger 2004). The clinical features of acute benzodiazepine intoxication include slurred speech, incoordination, unsteady gait, and impaired attention or memory; severe overdose may lead to stupor or coma. Psychiatric manifestations include inappropriate behavior, labile mood, and impaired judgment and social functioning. Physical signs include nystagmus and decreased reflexes.

Initial management of intoxication and overdose involves general supportive care, as for any clinically significant sedative intoxication, including maintenance of an adequate airway, ventilation, and cardiovascular function. Following stabilization of respiratory and cardiac function, activated charcoal should be given (Jones and Volans 1999). A benzodiazepine antagonist, flumazenil (Romazicon), is available for the treatment of acute benzodiazepine intoxication. How-

ever, it may not completely reverse respiratory depression, and it can provoke withdrawal seizures in patients with benzodiazepine dependence (Weinbroum et al. 1997).

Effects of Chronic Use

Ketamine and Phencyclidine

The long-term consequence most commonly associated with hallucinogen use is hallucinogen persisting perception disorder (HPPD), also known as "flashbacks" (see Chapter 51 in this volume). A flashback is an episode in which certain aspects of a previous hallucinogen experience are reexperienced unexpectedly (Weaver 2012a). These episodes last several seconds to several minutes and are self-limited. Triggers include stress, exercise, use of other drugs (especially marijuana), or entering a situation similar to the original drug experience; the flashbacks may also occur spontaneously. The unpredictability of HPPD often provokes anxiety when episodes occur, but episodes are fairly rare and tend over time to decrease in frequency, duration, and intensity as long as no additional hallucinogen is taken (Strassman 1984). Episodes are unlikely to occur more than 1 year after the original hallucinogen experience. Treatment of HPPD consists of supportive care, including reassurance. Benzodiazepines help reduce anxiety, but haloperidol can worsen HPPD (Moskowitz 1971).

Hallucinogen use may result in long-term psychiatric consequences such as anxiety, depression, or psychosis (Maxwell and Spence 2005). The risk of a prolonged psychiatric reaction depends on the user's underlying predisposition to develop psychopathology, the amount of prior hallucinogen use, the use of other drugs, and the dose and purity of the hallucinogen taken (Strassman 1984). Treatment of prolonged anxiety, depression, or psychosis is the same as when these conditions are not associated with hallucinogen use.

Methamphetamine and MDMA

An abstinence syndrome can occur with chronic stimulant use. Abrupt discontinuation of stimulants does not cause gross physiological sequelae. If marked depression persists longer than 1 week after withdrawal, the patient should be evaluated carefully to determine if he or she is "self-medicating" an underlying depression, which then should be treated with a specific antidepressant.

The clinical features of chronic stimulant use include depression, fatigue, poor concentration, and mild parkinsonian features such as myoclonus (inappropriate, spontaneous muscle contractions), tremor, or bradykinesia (slowing of movements). Chronic use of MDMA can lead to a paranoid psychosis that is clinically indistinguishable from schizophrenia; it is usually reversible after a prolonged drug-free state (Buchanan and Brown 1988). Several studies suggest that MDMA use (possibly in conjunction with marijuana) can lead to cognitive decline in otherwise healthy young people (Gouzoulis-Mayfrank et al. 2000); this neurotoxicity has been described to occur with typical recreational doses.

Gamma-Hydroxybutyrate

Some individuals have developed physiological dependence on GHB. Symptoms

of withdrawal include anxiety, tremor, insomnia, and "feelings of doom," which may persist for several weeks after stopping the drug (Galloway et al. 1997). Severe withdrawal involves agitation, delirium, and psychosis (McDaniel and Miotto 2001). GHB withdrawal is treated with benzodiazepines, which may need to be given in very high doses (Dyer et al. 2001). Antipsychotics or pentobarbital (Sivilotti et al. 2001) may have some utility in treatment of severe GHB withdrawal.

Flunitrazepam

Few data are available about long-term physiological and psychological consequences of intermittent, high-dose use of benzodiazepines in the setting of polysubstance abuse. Chronic use can result in a withdrawal syndrome that often requires detoxification with medication such as clonazepam or phenobarbital. Clinical features of long-term use of benzodiazepines are similar to acute features but may be accompanied by a dementia consisting of recent and remote memory loss (Weaver et al. 1999). Long-term use of benzodiazepines can worsen underlying depression and anxiety (Rickels et al. 1999).

Treatment of Club Drug Addiction

Treatment of club drug addiction involves similar components to that of other types of addiction, including behavioral components such as individual and group counseling with cognitive-behavioral therapy (CBT), motivational enhancement therapy, and 12-step self-help group facilitation. Adolescents and young adults are the primary club drug users, so family members should be part of the treatment program.

Problems reported by club drug users at admission and follow-up after addiction treatment are of comparable severity with those reported by patients who abuse alcohol, cocaine, or heroin (Maxwell and Spence 2005). Some club drug users need both mental health and addiction treatment, so clients should be assessed for depression and prescribed antidepressant medication where appropriate (Maxwell and Spence 2005).

Contingency management has proven effective in increasing the period of continuous abstinence from methamphetamine (Roll et al. 2006) as well as other substances of abuse (Lussier et al. 2006). Relapse prevention, a type of CBT, has been recommended for ketamine addiction (Jansen and Darracot-Cankovic 2001). Candidate medication studies for pharmacologic treatment of methamphetamine addiction include sertraline, bupropion, mirtazapine, modafinil, dextroamphetamine, ondansetron, risperidone, aripiprazole, baclofen, and gabapentin. However, no single medication has demonstrated consistent efficacy, and each trial contained a variety of methodological limitations (Brackins et al. 2011). A single case study showed that topiramate reduced MDMA euphoria and consumption (Akhondzadeh and Hampa 2005). A clinical trial of duloxetine demonstrated inhibition of effects of MDMA, including subjective drug effects, so this may be useful for treatment of addiction (Hysek et al. 2012).

Treatment of club drug addiction is challenging for several reasons. The club drugs consist of several different classes of substances, which vary in their psychological and physiological effects. Treatment is often difficult because of the young age of most users and concurrent polysubstance abuse. Clinicians should be knowledgeable of and prepared to

provide treatment for very different combinations (Maxwell and Spence 2005). The pattern of use is usually intermittent in social settings, so it may be perceived as less of a problem. Patients who chronically abuse phencyclidine display such characteristics as impulsiveness and poor interpersonal skills, which may make successful treatment more challenging, but a treatment environment with a supportive structure can be helpful.

Useful Web Sites

National Institute on Drug Abuse: www.clubdrugs.org
DanceSafe: www.dancesafe.org
Erowid: www.erowid.org

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CHAPTER 54

Stimulant-Related Disorders

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Cocaine and methamphetamine are psychostimulants that activate the central nervous system and produce powerful reinforcing effects (e.g., euphoria, elevated mood, and high) that contribute to their high addiction liability. Although significant advances were made in uncovering the neurobiological mechanisms underlying stimulant addiction, this new knowledge has yet to translate into effective pharmacotherapies for stimulant use disorder (Forray and Sofuoglu 2014). However, several effective behavioral interventions are available for the treatment of stimulant use disorder (Dutra et al. 2008). The pharmacological and behavioral treatment research has focused mainly on cocaine use disorder, and it is generally assumed that findings from these studies may also be generalized to the treatment of methamphetamine use disorder.

Pharmacotherapy

Agonist Approaches

As demonstrated by the effectiveness of methadone treatment for opioid use disorder, the main strategy of agonist treatments is to substitute a safer, longer-acting drug for the riskier, short-acting one. Consistent with the pharmacological effects of stimulants, the agonist treatment approach for stimulant use disorder has mainly targeted medications that increase synaptic dopamine levels in the brain reward circuit (Herin et al. 2010).

Amphetamines, which increase synaptic dopamine release by disrupting the storage of dopamine in intracellular vesicles and inhibiting the dopamine transporter, have shown some promise as agonist-like therapy for cocaine use disorder.

In randomized clinical trials, dextroamphetamine reduced drug use in short-term clinical trials in cocaine (Grabowski et al. 2004; Shearer et al. 2003) and methamphetamine (Longo et al. 2010; Shearer et al. 2001) users. Methamphetamine has also been shown to reduce cocaine use and craving in a placebo-controlled trial (Mooney et al. 2009). Methylphenidate, which, like cocaine, increases synaptic dopamine levels by inhibiting reuptake by monoamine transporters, has had limited success in patients with cocaine use disorder (Levin et al. 2007; Schubiner et al. 2002) and in one clinical trial reduced use among patients with amphetamine use disorder (Tiihonen et al. 2007). Overall, dextroamphetamine and methamphetamine seem to be more promising than methylphenidate as a treatment for stimulant use disorder. However, the long-term safety and efficacy of amphetamines as a treatment for stimulant use disorder remain to be determined.

Another example of an agonist approach for stimulant use disorder is modafinil, which acts as a weak dopamine transporter inhibitor and increases synaptic dopamine levels (Martinez-Raga et al. 2008). Initial clinical trials with modafinil were promising for cocaine and methamphetamine addiction (Dackis et al. 2005; Shearer et al. 2009). However, subsequent larger randomized clinical trials have been negative (Anderson et al. 2012; Dackis et al. 2012). Bupropion, which acts as a weak dopamine and norepinephrine reuptake inhibitor and enhances extracellular dopamine levels in the nucleus accumbens, has failed to show any significant effect for cocaine and heavy methamphetamine users but does reduce use among light methamphetamine users (Shoptaw et al. 2008a, 2008b). Interestingly, bupropion, when combined with contingency management, reduced cocaine use more effectively than either treatment alone or placebo (Poling et al. 2006).

Disulfiram is another medication that increases synaptic levels of dopamine, by inhibiting dopamine-β-hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine. In clinical trials for cocaine use disorder, disulfiram has been shown to decrease cocaine use independent of alcohol use (Carroll et al. 2004; Petrakis et al. 2000; Pettinati et al. 2008). A recent study also reported that cocaine users who have a genetic variation resulting in low DBH enzyme compared with those with normal activity are less likely to benefit from disulfiram treatment (Kosten et al. 2013). These findings provide further support for the potential efficacy of disulfiram for the treatment of cocaine addiction.

Medications Targeting Neuroadaptations Associated With Stimulant Addiction

Stimulant addiction is associated with neuroadaptive changes in brain dopamine, norepinephrine (NE), corticotrophin releasing factor, γ-aminobutyric acid (GABA), and glutamate. These neuroadaptations are thought to underlie the negative reinforcing effects of abstinence from drug use that are clinically observed as withdrawal symptoms, craving for drug use, and negative mood states such as dysphoria, irritability, and anxiety (Koob and Le Moal 2008).

Medications targeting NE have shown promising results for treatments that are aimed at stimulant withdrawal or relapse (Sofuoglu and Sewell 2009). Human clinical laboratory studies suggest that lofexidine, an α_2-adrenergic agonist, may

attenuate stress-induced relapse in cocaine and opioid users (Highfield et al. 2001; Sinha et al. 2007). Preliminary results from a clinical study using guanfacine, an α_2-adrenergic agonist, showed attenuated cue-induced cocaine craving in individuals with cocaine use disorder (Fox et al. 2012). Clinical trials are under way to test the efficacy of guanfacine and carvedilol, an α- and β-adrenergic antagonist, for stimulant use disorder.

There is growing interest in the role of glutamate in stimulant addiction. *N*-acetylcysteine (NAC), a medication used for the treatment of acetaminophen (Tylenol) overdose, targets brain glutamate. NAC's proposed mechanism of action is the normalization of extracellular glutamate levels in the nucleus accumbens by stimulating the cysteine/glutamate antiporter (Baker et al. 2003). NAC has shown some positive results in small clinical trials for cocaine use disorder (Adewale et al. 2006; Baptista et al. 2004). Larger studies are under way to test NAC's efficacy for the treatment of stimulant use disorder.

Medications targeting GABA activity have also been investigated for stimulant use disorder. Vigabatrin (γ-vinyl-GABA) is an irreversible inhibitor of GABA transaminase that has been shown to reduce cocaine-induced dopamine release in laboratory animals. In a randomized controlled trial, vigabatrin led to a higher percentage of subjects achieving and maintaining abstinence from cocaine and alcohol (Brodie et al. 2009). However, preliminary results from a large follow-up clinical trial do not support these findings. The final results are still pending. Topiramate, another antiseizure medication with GABAergic effects, has demonstrated potential for the treatment of stimulant addiction. In a placebo-controlled clinical trial, topiramate improved abstinence rates in patients with cocaine use disorder compared with placebo (Kampman et al. 2004). In a multisite placebo-controlled trial with methamphetamine users, although topiramate did not improve abstinence rates, it reduced the amount of methamphetamine used weekly and reduced relapse rates of those already abstinent (Elkashef et al. 2012). A recent clinical trial tested the combination of topiramate with extended-release mixed amphetamine salts (MAS-ER) as a treatment for cocaine addiction. Subjects who were randomly assigned to receive topiramate or topiramate plus MAS-ER achieved greater rates of abstinence compared with placebo (Mariani et al. 2012). These promising findings need to be tested in future clinical trials.

Medications Targeting Cognitive Deficits

Current evidence indicates that most forms of chronic drug use, including cocaine or methamphetamine use, may be associated with significant cognitive impairments, especially in attention, working memory, and response inhibition functions (Sofuoglu et al. 2013). These impairments may be predictive of poor treatment retention and outcome in stimulant users. Medication treatments targeting these impaired cognitive functions may be a novel treatment strategy for stimulant addiction (Sofuoglu 2010). Cognitive enhancement strategies may be especially important early in the treatment, improving the ability to learn, remember, and implement new skills and coping strategies.

There are many potential cognitive enhancers, including cholinesterase inhibitors, modafinil, amphetamines, partial nicotinic acetylcholine receptor (nAChR) agonists such as varenicline, and metabotropic glutamate agonists (Sofuoglu et al. 2013). Among cholinesterase inhibitors, galantamine is one with additional allo-

steric potentiator effects at the α_7 and $\alpha_4\beta_2$ nAChR. In a recent double-blind placebo-controlled study, galantamine treatment improved sustained attention and working memory functions in abstinent cocaine users (Sofuoglu et al. 2011). In a separate double-blind study of individuals with opioid and cocaine use disorder, those receiving galantamine submitted fewer cocaine-positive urine specimens and reported less cocaine use than those assigned to placebo (Sofuoglu and Carroll 2011). Randomized clinical trials are under way to test the efficacy of galantamine for the treatment of cocaine addiction.

Immunotherapies

By developing antibodies that bind the drug of abuse following its use, immunotherapies reduce the amount of drug that reaches the brain and attenuate its rewarding effects. The most promising use of vaccines will be to prevent relapse in individuals whose drug use is limited to a single agent because the antibodies produced are specific for a given drug of abuse, which will limit their clinical efficacy in polysubstance users. Following the encouraging results from a placebo-controlled clinical trial of an anti-cocaine-addiction vaccine (Martell et al. 2009), a multisite clinical trial for the vaccine is currently under way.

Gender-Specific Treatments

Accumulating evidence suggests that the female sex hormones estradiol and progesterone have wide-ranging effects on brain functioning, including the rewarding effects of stimulant drugs. In women with cocaine use disorder, those who were in the luteal phase (high progesterone) of their menstrual cycle had attenuated responses to the subjective effects of cocaine compared with those who were in the follicular phase (high estradiol, low progesterone) of the menstrual cycle (Sofuoglu et al. 1999). Consistent with these findings, oral progesterone treatment attenuated the subjective effects from repeated cocaine deliveries (Evans and Foltin 2006; Sofuoglu et al. 2002).

Pregnancy, which is characterized by high circulating progesterone levels, is associated with decreased substance use. Unfortunately, drug use increases again after delivery (Yonkers et al. 2012). The incremental decrease in drug use over the course of pregnancy as progesterone levels increase and the escalation in drug use after delivery when progesterone levels drop suggest the possibility that progesterone influences drug use during this period. A double-blind, randomized, placebo-controlled study is under way to evaluate the efficacy of oral progesterone in reducing cocaine use among postpartum women with a history of cocaine use.

In summary, the development of effective medications for stimulant use disorder remains an area of active research (Table 54–1). So far, there are no medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of stimulant use disorder.

Behavioral Therapies

Behavioral therapies are an essential component of treatment of stimulant use disorder. Several behavioral treatments have been used, including cognitive-behavioral therapy (CBT), individual drug counseling, and contingency management (CM). In contrast to the selective effects of pharmacotherapies for individual drugs of abuse, behavioral treatments are not specific for a given addiction and

TABLE 54–1. Summary of promising pharmacotherapies for the treatment of stimulant use disorder

Treatment target	Agent	Mechanism of action	Efficacy
Agonist approach	Amphetamines	Stimulation of vesicle release and reverse dopamine transporter (DAT)	Reduced drug use in short-term clinical trials in cocaine and methamphetamine users
	Modafinil, bupropion	DAT inhibitors	No significant reduction in cocaine use with modafinil compared with placebo Bupropion effective only in light methamphetamine users
	Disulfiram	Dopamine-β-hydroxylase inhibitor	Effective in decreasing cocaine use clinically
Neuroadaptations associated with stimulant addiction	Lofexidine	α_2-adrenergic receptor agonist	Attenuates stress-induced relapse in cocaine users
	Carvedilol	α- and β-adrenergic receptor antagonist	Clinical trial under way
	Guanfacine	α_2-adrenergic receptor agonist	Clinical trial under way; preliminary results show attenuated cue-induced cocaine craving
	N-acetylcysteine	Stimulation of cystine/glutamate antiporter	Positive results in small clinical trials for cocaine use disorder
	Vigabatrin	GABA transaminase irreversible inhibitor	Mixed results, with some clinical trials showing higher percentage of subjects achieving and maintaining abstinence from cocaine compared with placebo but not others
	Topiramate	Enhancement of GABA and inhibi-	Promotes abstinence in cocaine users and reduces amphetamine us-

TABLE 54–1. Summary of promising pharmacotherapies for the treatment of stimulant use disorder *(continued)*

Treatment target	Agent	Mechanism of action	Efficacy
Cognitive deficits associated with stimulant addiction	Galantamine and other cognitive enhancers	Acetylcholinesterase inhibitor, allosteric potentiator of acetylcholine receptor	Improved sustained attention and working memory functions in abstinent cocaine users
Immunotherapies	TA-CD	Cocaine vaccine	Currently in phase IIB trial
Gender specific	Micronized progesterone	Exact mechanism unknown; possible GABA agonist and σ antagonist effects	In women with cocaine use disorder, progesterone attenuates cravings for and subjective positive response to cocaine
Psychiatric comorbidity	Antidepressants and other psychotropic medications	Monoamine reuptake inhibition and other mechanisms	Mixed results on stimulant use outcomes with antidepressant medications

can be effective for a range of addictions. These therapies provide a platform for pharmacological treatments by engaging the patient in the treatment and facilitate more long- term changes, including prevention of relapse (Carroll et al. 2004). A meta-analysis found a small to medium effect size, about 0.3 according to Cohen's standards, for CBT for cocaine use disorder (Dutra et al. 2008). CM treatments generally lead to moderate to high effect sizes, 0.58 or higher (Dutra et al. 2008). However, these treatment effects wear off rapidly following the termination of the CM treatment.

The goal of CBT is to teach coping and cognitive strategies to prevent drug use behavior. Social skills and relapse prevention are also successfully added to CBT for cocaine and methamphetamine use disorder. The mechanism of CBT's efficacy may involve strengthening executive control over behavior, as there is some evidence that acquisition of these types of skills in CBT mediates long-term outcomes. The efficacy of CBT for cocaine addiction has been demonstrated in multiple studies. A recent advance in this area has been the development of computerized CBT for cocaine addiction (Carroll et al. 2008). The computerized CBT allows personalizing the pace of treatment delivery and repeating the material if needed on the basis of the patient's individual needs.

CM has also been widely used for the treatment of cocaine and methamphetamine use disorder (Higgins et al. 2000; Stitzer and Petry 2006). CM aims to reduce behavior maintained by drug reinforcers and to increase behavior maintained by nondrug reinforcers. This goal is achieved by offering rewards such as vouchers contingent on drug abstinence (i.e., drug-free urine samples). Two steps are critical for successful implementation of CM. First, the target behavior (e.g., clean urine samples) has to be reliably detected with frequent monitoring (e.g., urine testing three times a week). Second, on observation of the target behavior, a tangible reinforcer such as a voucher is provided without any delay. Many studies have shown the efficacy of CM in individuals addicted to cocaine or methamphetamine (Dutra et al. 2008). Most studies using CM have been conducted in research settings. The implementation of CM in clinical settings remains to be further developed.

Psychiatric Comorbidity

Among treatment-seeking stimulant users, primary psychiatric disorders, including schizophrenia, mood and anxiety disorders, and attention-deficit/hyperactivity disorder (ADHD), are common (Ford et al. 2009). Patients with comorbid substance use disorders and psychiatric disorders usually have poorer outcomes than those without comorbidity. One of the possible mechanisms underlying this high comorbidity is self-medication, in which individuals with primary psychiatric disorders use drugs or alcohol to relieve specific symptoms, such as negative affect, or side effects of their treatment medications, such as sedation. Alternatively, common underlying factors may lead to high comorbidity between primary psychiatric disorders and drug addiction (Chambers et al. 2001). Common vulnerability factors may include impulsivity, increased reward sensitivity, and cognitive deficits, including attention, working memory, or response inhibition.

Several clinical trials of treatments targeting both stimulant addiction and comorbid conditions yielded mixed results. In depressed stimulant users, desipramine (McDowell et al. 2005) or imipra-

mine (Nunes et al. 1995) reduced depressive symptoms, cocaine use, and craving. In contrast, others reported that fluoxetine treatment was not more effective than placebo in reducing depressive symptoms or cocaine use (Schmitz et al. 2001). In depressed cocaine users, a combination of CBT and desipramine improved treatment retention and abstinence, emphasizing the importance of combining pharmacotherapy and behavioral interventions for the treatment of depressed stimulant users (Carroll et al. 1995). Methylphenidate treatment in stimulant users with ADHD led to improvement in ADHD symptoms without affecting cocaine (Schubiner et al. 2002) or amphetamine (Konstenius et al. 2010) use. However, in another clinical trial, treatment with methylphenidate reduced cocaine use in stimulant users with ADHD when there was improvement in the ADHD symptoms (Levin et al. 2007).

Treatment Guidelines

Treatment for stimulant use disorder requires a comprehensive assessment of the patient's psychiatric and medical problems. Moreover, because information obtained from an individual addicted to drugs may be incomplete or unreliable, it is important that the patient receive a thorough physical, including blood and supervised urine samples for analysis.

Similar to the treatment of other addictions, treatment for stimulant addictions can be divided into three phases: detoxification, initial recovery, and relapse prevention. The first phase, *detoxification,* has the goal of achieving abstinence that is sufficiently sustained to yield a safe reduction in immediate withdrawal symptoms. Stimulant withdrawal is characterized by mild depressive symptoms and clinically does not require specific treatment. The clinician needs to be aware that among stimulant users polydrug use is common. Patients may ingest large amounts of one or more drugs at potentially lethal doses, and therefore it is important that the physician be aware of the dangers of possible drug combinations, such as cocaine and alcohol or heroin. The management of stimulant intoxication typically requires only supportive care. However, hypertension, tachycardia, chest pain, and seizures can occur with cocaine intoxication and may require specific treatment. The use of β-adrenergic antagonists for the acute treatment of cocaine-associated chest pain and myocardial infarction should be avoided because it can lead to unopposed α adrenergic stimulation, coronary vasoconstriction, and myocardial ischemia. Agitation and persecutory delusions may also be seen with stimulant intoxication and can be managed with benzodiazepines or antipsychotics.

The second phase, *initial recovery,* has goals of developing sustained motivation to avoid relapse, learning strategies for tolerating craving induced by external or internal cues, and developing new patterns of behavior that entail replacement of drug-induced reinforcement with alternative rewards. This can be accomplished through CM and CBT approaches. Although there are no FDA-approved treatments for stimulant use disorders, medications that block or reduce drug rewards and reduce craving by substituting for drug effects can aid this process. Cessation of drug use may also allow a clearer assessment for the presence of common comorbid conditions, including mood or anxiety disorders and cognitive impairments. Evidence suggests that simulant users experience cognitive problems during early abstinence from stimulant use (Woicik et al. 2009). Medications targeting cognitive deficits, if proven effective in

large clinical trials, might be useful in this phase of treatment by improving the ability to learn and implement new skills and coping strategies.

The third phase, *relapse prevention,* takes place after a period of sustained abstinence and requires subjects to develop long-term strategies that will allow them to replace past drug behaviors with new, healthy behaviors. Success at this phase can be enhanced by behavioral treatments aimed at sustaining motivation and facilitating effective execution of skills learned during recovery initiation. Medications that target the neuroadaptations associated with stimulant addiction may be used to attenuate relapse.

Recommended Readings

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CHAPTER 55

Nicotine-Related Disorders

Robert M. Anthenelli, M.D.

With nearly one out of two cigarettes consumed in the United States smoked by individuals with psychiatric and substance use disorders (Lasser et al. 2000), it is fitting that the new edition of this textbook includes a chapter on tobacco.

In this chapter, I first examine the mental health smoking epidemic, including its costs and contributing factors, and psychiatry's historical reluctance to address and treat tobacco addiction. I also sketch the neurobiology of nicotine dependence, focusing on tobacco smoke's highly addictive properties. Then, I discuss ways to implement an approach for screening patients who smoke, advising them to quit, and assessing which patients are motivated to stop. General principles about first- and second-line treatments are described along with the importance of combining counseling with pharmacotherapy to maximize success. Finally, I sketch some of the nuances of treating this special population of smokers, focusing on patients with mood, anxiety, psychotic, and addictive disorders.

The Mental Health Smoking Epidemic and Its Costs

Individuals with psychiatric and substance use disorders (PSUD) consume roughly 45% of the cigarettes sold in the United States (Grant et al. 2004; Lasser et al. 2000). This translates into approximately 175 billion cigarettes purchased and nearly $40 billion in annual sales (Hall and Prochaska 2009). Although rates of smoking in the general population have significantly declined over the past 50 years since the first surgeon general's report warning about smoking-related health risks, a commensurate decrease among smokers with PSUD has not been observed.

Figure 55–1 depicts the prevalence rates of smoking in patients with PSUD com-

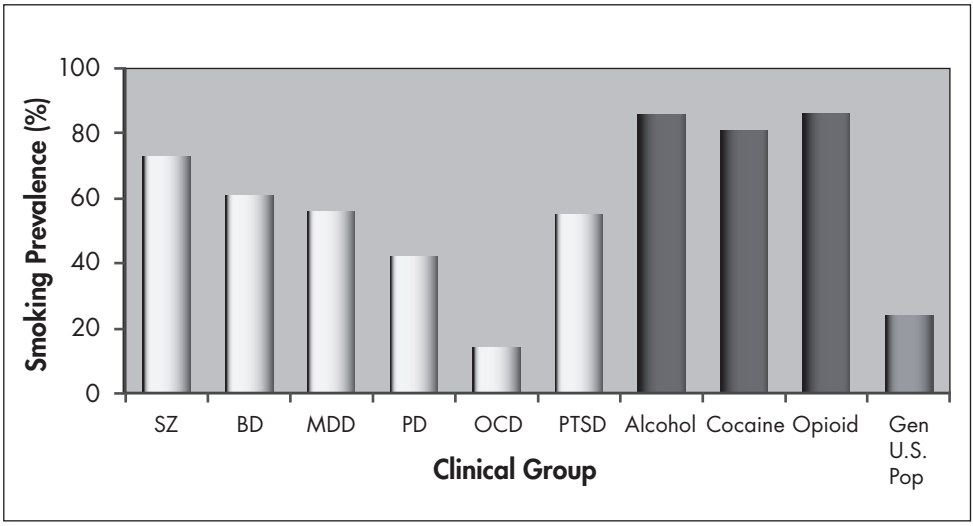

FIGURE 55–1. Prevalence of smoking in individuals with psychiatric and substance use disorders.
BD=bipolar disorder; MDD=major depressive disorder; OCD=obsessive-compulsive disorder; PD=panic disorder; PTSD=posttraumatic stress disorder; SZ=schizophrenia and schizoaffective disorder.
Source. Adapted from Kalman et al. 2005.

pared with rates in the general U.S. population (Kalman et al. 2005). In general, individuals with mental disorders smoke at rates two to four times that of women and men without psychiatric disorders (Kalman et al. 2005). Rates are highest among individuals with serious mental disorders such as schizophrenia, schizoaffective disorder, and bipolar disorder and among women and men with substance use disorders (see Figure 55–1). However, such common disorders as major depressive disorder (smoking prevalence 40%–60%), generalized anxiety disorder (approximately 55%), and posttraumatic stress disorder (PTSD; approximately 45%–65%) are also marked by high rates of smoking.

That smoking has been endemic in patients with PSUD most likely contributes to the excessive mortality rates observed among patients with serious mental illness (SMI). Individuals with SMI die decades earlier than age-matched general population cohorts (Colton and Manderscheid 2006). Not surprisingly, the leading causes of death in these individuals are smoking related, with most patients dying from heart disease, cancer, or cerebrovascular or respiratory disease.

Factors Contributing to the Smoking Epidemic

Multiple factors have contributed to the alarmingly high rates of smoking among individuals with PSUD. The 30-year lag between the 1964 surgeon general's report and publication, in 1996, of the American Psychiatric Association (APA) clinical practice guideline that first addressed smoking in psychiatric patients set the field behind. For example, one survey examining the proportion of psychiatric office visits in which any mention

of patients' smoking status was discussed revealed that nicotine dependence was addressed in only 12.4% of encounters (Himelhoch and Daumit 2003). However, even after treatment of tobacco dependence was included among the standards of care for psychiatrists, there was evidence that mental health providers missed most opportunities to intervene in the progression of the disorder. In fact, even among patients with PSUD, primary care physicians were found to provide smoking cessation counseling more often than did psychiatrists (Thorndike et al. 2001).

Despite abundant data to the contrary, there is also a misconception among some providers that quitting smoking with the use of approved techniques (see section "General Principles on Treating Nicotine-Related Disorders") will exacerbate psychiatric symptoms or, in the case of substance abusers, sabotage efforts at abstinence. These myths, combined with the field's underappreciation of the mental and physical health risks of chronic smoking, psychiatrists' inadequate training in treating nicotine and other drug dependence, and low incentives to take on this task, all create barriers to effective treatment of tobacco addiction treatment among mental health professionals (Hall and Prochaska 2009).

In addition to these provider-level variables, several factors working at the patient level have also contributed to the persistently high rates of smoking among patients with PSUD. First, there is some evidence that the tobacco industry has courted this important segment of its business (see Hall and Prochaska 2009 for review). Second, although the practice is changing with the movement toward smoke-free treatment environments, cigarettes have been used in the past as rewards for certain behaviors among psychiatric inpatients. Third, there has been an overreliance on the self-medication hypothesis as a rationale to explain continued cigarette use. Thus, when individuals smoke to ameliorate symptoms of nicotine withdrawal, this practice has been misinterpreted and viewed as if smoking improves the underlying mental health condition. Fourth, patients with psychiatric disorders frequently lack strong nonsmoking social support systems, making it more challenging to succeed when they attempt to quit. Finally, because patients with PSUD tend to start smoking earlier and smoke more heavily than individuals without mental disorders, they are highly nicotine dependent.

Tobacco Addiction

The tendency for some smokers with PSUD to start smoking earlier and more heavily increases their proneness to developing tobacco addiction. Although beyond the scope of this clinically focused chapter, here I sketch the basics of the tobacco addiction process that underpin the concept of a tobacco use disorder as specified in DSM-5 (American Psychiatric Association 2013).

Like the other substances in use disorders covered in this textbook, nicotine and other components in tobacco smoke commandeer the brain's reinforcement system rooted in the mesocorticolimbic dopamine circuitry (Anthenelli 2005). Nicotinic acetylcholine receptors (nAChRs) located on 1) dopamine cell bodies in the ventral tegmental area, 2) the terminals of excitatory glutamatergic inputs synapsing on these dopamine neurons, and 3) the cell bodies of γ-aminobutyric acid inhibitory inputs bind nicotine and, in a complex process, trigger the release of dopamine in the nucleus accumbens (NAcc). Depending on the regional circuits in-

volved, this neurochemical process underlies the individual's *learning to smoke* and *wanting to smoke* constructs that characterize nicotine addiction. That is, smoking invokes a long-term potentiation undergirding the memorization of the smoking behaviors, and the release of dopamine in the NAcc reinforces those behaviors. These facets of the addiction process are sometimes described as positive reinforcement.

With chronic, repeated use of nicotine, however, an opponent process takes hold: chronic nicotine administration causes a marked upregulation of nAChRs, which is thought to contribute to the drug's negative reinforcing effects. This multistep process, which results from nicotine's tendency to desensitize or inactivate nAChRs, begins to manifest when nicotine is no longer present, such as when an individual tries to quit "cold turkey." In the absence of nicotine these receptors reactivate, and the ensuing outflow of these excitatory signals is thought to underlie aspects of the tobacco withdrawal syndrome. Thus, to feel normal again and to ameliorate the withdrawal symptoms, the smoker relapses. It is in this regard that smokers "need to smoke."

This oversimplification of the complex brain processes underlying nicotine addiction has heuristic value in understanding nicotine use disorder as described in the APA's recently released DSM-5 (American Psychiatric Association 2013).

General Principles on Treating Nicotine-Related Disorders

With so many psychiatric patients smoking and dying from tobacco-related diseases, it is important for mental health providers to realize that intervening in this deadly addiction is part of our standard of care. After one accepts the notion that helping psychiatric patients quit smoking is part of one's job, applying the general principles outlined below can become a rewarding and fulfilling part of psychiatric clinical practice.

Brief Interventions

Effective smoking cessation treatment begins with utilizing the "5As" brief intervention with all PSUD patients (see Figure 55–2). Simplified derivations of this brief intervention also exist. Thus, McRobbie (2008) has coined the mnemonic "ABC": Ask about smoking status, give Brief advice to stop smoking, and provide evidence-based Cessation support. The American Academy of Family Physicians has espoused the Ask and Act program in an effort to further streamline this process. Regardless of the memory tool chosen, it is clear that even 2–3 minutes spent addressing this problem with one's patients can have a positive impact.

As alluded to earlier (see section "Factors Contributing to the Smoking Epidemic"), one misconception among some mental health practitioners is that psychiatric patients do not want to quit smoking. In fact, PSUD patients in both outpatient and inpatient mental health settings do want to quit, with surveys indicating that roughly 40% are in the contemplation stage of change (i.e., contemplating quitting in the next 6 months but not in the next month) and approximately 25% are in the preparation stage (i.e., they have plans to quit in the next 30 days). For those patients in the precontemplation stage of change who do not plan to quit in the next 6 months and for the contemplators, one should utilize the "5 Rs" to motivate tobacco users to

1. **A SK** – **Systematically identify all tobacco users at every visit.**
2. **A DVISE** – **Strongly urge all tobacco users to quit.**
3. **A SSESS** – **Determine willingness to make a quit attempt.**
4. **A SSIST** – **Aid the patient in quitting.**
5. **A RRANGE** – **Schedule follow-up contact.**

FIGURE 55–2. The "5As" for brief intervention in tobacco users.

quit (Fiore 2008). This counseling approach borrows elements from Miller and Rollnick's (1991) motivational interviewing therapeutic technique. Thus, at each visit, the clinician should lead the patient in a brief discourse on the Relevance (for the individual) of quitting smoking, the Risks of continued smoking, the potential Rewards associated with quitting, the Roadblocks he or she experienced in previous unsuccessful attempts at quitting, and Repetition of the motivational interview.

FDA-Approved First-Line Smoking Cessation Medications

Currently, there are three types of medications approved by the U.S. Food and Drug Administration (FDA) as aids to smoking cessation: nicotine replacement therapy (NRT), bupropion sustained release (bupropion SR), and varenicline.

Nicotine Replacement Therapy

The five FDA-approved formulations of NRT share a common mechanism of action in that each substitutes nicotine for smoking. These formulations differ by their route of administration, which, in turn, influences the pharmacokinetic profile of each agent. Nicotine replaced via a transdermal delivery system (i.e., nicotine patches) has the advantage of a slower, longer-acting profile compared with the faster-acting but more short lived preparations found in nicotine gum, lozenges, and inhalers (Rigotti 2002). The fastest-acting nicotine nasal spray best mimics smoking a cigarette; however, none of the NRTs can match the nicotine delivered to the brain via the combustible, inhaled route, probably limiting their effectiveness.

Table 55–1 provides an overview of the typical daily dosage, treatment duration, and common side effects of the five formulations of NRT. Nicotine gum, lozenges, and patches are available over the counter, but the spray and inhaler are prescription only.

The overall risk ratio (RR) for abstinence for any form of NRT compared with a control condition (i.e., placebo or no NRT in a clinical trial) is 1.58 (95% confidence interval [CI]=1.50–1.66) (Stead et al. 2012). Given this relatively modest quit rate, there is increasing utilization of combination NRT, which is typically accomplished by combining one of the short-acting preparations (e.g., gum, lozenge, or spray) with the longer-acting patch (Fiore 2008). Such combination

TABLE 55–1. FDA-approved first-line smoking cessation aids

Medication	Dosage	Length of treatment	Side effects	Contraindications
Nicotine gum 2 mg (if first cigarette smoked >30 minutes after awakening) 4 mg (if first cigarette smoked <30 minutes after awakening)	1 piece/hour up to maximum of 24 pieces per day	6–12 weeks; taper weeks 7–12	Mouth soreness, hiccups, dyspepsia, and jaw ache	FDA pregnancy class D agent Caution in patients immediately (within 2 weeks) post-MI and in those with arrhythmias or with unstable angina
Nicotine patch 7, 14, or 21 mg	Step-down versus single dosage (per 24-hour duration) Single dosage: 21 or 14 mg (for lighter smokers) Step-down: 4 weeks at 21 mg, then 2 weeks at 14 mg, then 2 weeks at 7 mg	4 weeks for step-down dosage	Sleep disturbance and local skin reaction (up to 50%); reaction may result in discontinuation of patch in 5% of patients	FDA pregnancy class D agent Same as nicotine gum
Nicotine inhaler 4 mg/cartridge	6–16 cartridges/day	6 months then gradual taper for last 3 months	Mouth and throat irritation (40%), coughing (32%), and rhinitis (23%)	FDA pregnancy class D agent Same as nicotine gum
Nicotine nasal spray 1 dose=1 spray (0.5 mg per spray to each no	1–2 doses/hour; minimum: 8 doses/day;	3–6 months	Moderate to severe nasal irritation for first 2 days	Contraindicated in patients with severe reactive airway disease ne gum

TABLE 55–1. FDA-approved first-line smoking cessation aids *(continued)*

Medication	Dosage	Length of treatment	Side effects	Contraindications
Nicotine lozenge 2 mg (for smokers with first cigarette >30 minutes after waking) 4 mg (for smokers with first cigarette within 30 minutes of waking)	1 every 1–2 hours first 6 weeks, then 1 every 2–4 hours during weeks 7–9, then 1 every 4–8 hours during weeks 10–12	12 weeks	Nausea, hiccups, heartburn, headaches, and coughing	Has not been evaluated by FDA for teratogenicity Same as nicotine gum
Bupropion SR 150 mg	Begin 1–2 weeks before quit date: 150 mg qam for 3 days, then 150 mg bid for 12 weeks	12 weeks but may continue for 6 months after quitting	Insomnia (35%–40%) and dry mouth (10%)	FDA pregnancy class C agent Contraindicated in patients with history of seizures or eating disorders and those who have used MAOIs the last 14 days Boxed warning to monitor for neuropsychiatric adverse events
Varenicline 0.5 mg 1 mg	Begin 1 week before quit date: 0.5 mg po qd for 3 days, then 0.5 mg po bid for 4 days, then 1 mg po bid for 3 months	Up to 6 months	Nausea, insomnia, and abnormal dreams	FDA pregnancy class C agent Caution in patients with renal impairment Boxed warning to monitor for neuropsychiatric adverse

treatments have been found to produce higher 6-month abstinence rates (odds ratio=1.9) (Fiore 2008), and this off-label recommendation should be considered in PSUD smokers who typically smoke more heavily and have more severe levels of nicotine dependence.

Bupropion Sustained Release

Bupropion is an antidepressant medication that was approved as an aid to smoking cessation in 1997 and since then has gone on to be one of the most durable treatments for tobacco dependence. For many years it was thought that as an inhibitor of both the dopamine and norepinephrine transporters, bupropion SR's main mechanism of action was boosting synaptic levels of these catecholamine neurotransmitters, thereby ameliorating symptoms of nicotine withdrawal and reducing craving (Fiore 2008). However, preclinical studies have demonstrated that bupropion also works as a nonselective nAChR antagonist, and these blockade effects most likely contribute to its efficacy (Mansvelder et al. 2007).

Table 55–1 highlights the dosing scheme, common side effects, and precautions and contraindications for bupropion SR as an aid to smoking cessation. Unlike NRTs, which are typically started on the target quit date (i.e., the day on which the individual actually tries to stop smoking), this medication requires an upward titration to reduce side effects and achieve steady state concentrations in the week(s) prior to the target quit date.

Combining bupropion SR and transdermal NRT was tested in one multicenter trial that also included placebo, nicotine patch, and bupropion SR monotherapy arms (Jorenby et al. 1999). It was found that the bupropion SR plus patch combination and bupropion SR monotherapy significantly improved quit rates compared with placebo and that combination treatment was better than patch alone. However, although quit rates were highest among users of the combination, they were not statistically significantly better than monotherapy bupropion SR. Despite this negative statistical finding, in practice, combination bupropion SR and NRT is fairly widely used in patients with treatment-resistant dependence.

Varenicline

In 2006, the FDA approved the second nonnicotine medication as an aid to smoking cessation, varenicline tartrate. Specifically designed to target the $\alpha_4\beta_2$ type of nAChR, which was found to play an important role in nicotine's reinforcing effects (Coe et al. 2005), varenicline distinguishes itself from the other smoking cessation aids by working as a partial agonist. That is, treatment with varenicline partially stimulates dopaminergic neurons, thus ameliorating aspects of nicotine withdrawal, while at the same time the medication blocks nicotine from binding to this receptor subtype. This second aspect of the partial agonism is believed to make nicotine less reinforcing in instances when a smoker slips or lapses to smoking. In addition to these unique pharmacodynamic properties, varenicline is primarily excreted by the kidneys, with relatively few known drug-drug interactions (Obach et al. 2006).

In head-to-head comparisons with bupropion SR and placebo, varenicline was found to significantly increase quit rates compared with both the active and sham comparators (Gonzales et al. 2006; Jorenby et al. 2006). In another pivotal trial (Tonstad et al. 2006), 12 weeks of additional varenicline treatment (24 weeks total) in those who quit smoking initially

was found to reduce relapse to smoking. Table 55–1 sketches the dosing schedule, side effects, and other clinical features of varenicline in relation to NRT and bupropion SR.

Second-Line Medications for Smoking Cessation

In addition to the first-line medications, Fiore (2008), in an updated clinical practice guideline on treating tobacco use and dependence, recommended two non-FDA-approved medications for the treatment of tobacco dependence: nortriptyline and clonidine. The antidepressant nortriptyline has been found to be effective in smokers without psychiatric disorders and in individuals with histories of major depression (Hall et al. 1998). The antihypertensive agent clonidine has modest effects as a smoking cessation aid (Glassman et al. 1988). Both medications have dry mouth, sedation, and dizziness listed among their side effects, and these agents are best used in smoking cessation clinics and in treatment-resistant patients in whom first-line treatments have failed.

Combining Pharmacotherapy With Counseling

FDA-approved smoking cessation aids work best when combined with evidence-based behavioral counseling for tobacco dependence. There also appear to be dose-dependent effects with the evidence-based therapies. For example, Hughes (2000) reviewed the literature examining quit rates in smokers receiving no medication or therapy (approximately 5% of smokers quit smoking "cold turkey"), only brief therapy (approximately 2–3 minutes of brief intervention; approximately 10% of smokers quit smoking), and more intensive therapy (longer than 10 minutes of evidence-based counseling such as cognitive-behavioral therapy; approximately 15% of smokers quit smoking) (Hughes 2000). However, when these behavioral interventions were combined with either NRT or bupropion SR, quit rates doubled to 20% for brief therapy and 30% for intensive therapy.

Tailoring Treatments for Smokers With PSUD

In general, the evidence-based medications and behavioral interventions described earlier that have been widely tested in smokers without mental disorders and found to work are also effective in smokers with PSUD (Fiore 2008). However, fewer trials have been conducted in these special populations (Fiore 2008), quit rates are generally lower depending on the subgroup of psychiatric patients treated (Williams and Foulds 2007), and approaches need to be modified somewhat in consideration of the special characteristics of smokers with PSUD. Below we discuss strategies to tailor smoking cessation treatment for different categories of smokers with PSUD.

Smokers With Schizophrenia and Schizoaffective Disorder

Although evidence is mixed regarding the effectiveness of NRT in smokers with schizophrenia (George et al. 2000), the older studies on which this impression was based did not include more recent work utilizing higher-dose NRT combinations better aimed at this highly dependent subgroup of smokers. In contrast, there is good evidence that bupropion SR improves quit rates in smokers with schizophrenia, with one meta-analysis (Tsoi et al. 2013) finding end-of-treatment quit rates (RR=3.03; 95% CI=1.69–

5.42) and 6-month point prevalence abstinence rates (RR=2.8; 95% CI=1.02–7.58) significantly greater than those for placebo.

Evidence from uncontrolled open-label trials (Pachas et al. 2012) and a preliminary randomized, double-blind, placebo-controlled trial (Williams et al. 2012) indicates that varenicline also appears to be effective in smokers with schizophrenia or schizoaffective disorder. Regarding the randomized controlled trial (RCT), 19% of varenicline-treated participants compared with 4.7% of the placebo group achieved 7-day point prevalence abstinence at the end of the 12-week treatment period ($P<0.05$) (Williams et al. 2012). As was the case for trials with NRT and bupropion SR, the medication was generally well tolerated, with no exacerbation of positive or negative symptoms. However, regardless of the medication utilized, all studies conducted to date in smokers with schizophrenia are marked by high relapse rates after treatment has ended. Thus, specialty programs catering to this group will frequently use medications for longer durations than typically indicated, involve patients in extended intratreatment and extratreatment group support, or enroll patients in integrated mental health and tobacco dependence treatment programs (Williams and Foulds 2007; Ziedonis et al. 2008).

Smokers With Mood Disorders

Major depressive disorder is overrepresented among smokers to the extent that nearly one out of two smokers seeking treatment has a history of depression (Tsoh et al. 2000). NRT (Kinnunen et al. 2008), bupropion SR (Hayford et al. 1999), and nortriptyline (Hall et al. 1998) have all been found to be effective in smokers with a history of depression. However, as is the case with smokers with serious mental disorders, relapse rates are high (Brown et al. 2007), leading some smoking cessation specialists to prolong or combine treatments.

In one of the few studies conducted in subjects with stably treated current or recently remitted depression, the majority of whom were prescribed antidepressant medications, we found that varenicline is also efficacious as a smoking cessation aid in this subgroup of smokers (Anthenelli et al. 2013). Approximately 36% of subjects treated with varenicline quit smoking for the last 4 weeks of this 12-week trial compared with 15.6% in the placebo group (odds ratio=3.4; CI=2.2–5.2), and this beneficial effect persisted up to 1 year posttreatment initiation. Importantly, similar to prior trials with bupropion SR or nortriptyline, the medication did not exacerbate depressive symptoms.

Although smoking rates are high (50%–65%) among individuals with bipolar disorder, very few controlled smoking cessation trials have been conducted in this group (Heffner et al. 2011). Heffner et al. conducted a pilot study in 10 smokers with bipolar disorder, all of whom received open-label NRT and a specially designed psychosocial intervention, and found that 20% were able to quit smoking (Heffner et al. 2013). Among the participants, nonadherence with study medication and mood flare-ups were observed in 56% and 20%, respectively, leading the authors to recommend compliance enhancement and careful mood monitoring strategies when helping bipolar patients to quit.

Smokers With PTSD and Anxiety Disorders

Rates of smoking are elevated compared with the general population in individuals with PTSD, generalized anxiety dis-

order, panic disorder, or social phobia (Kalman et al. 2005). However, among these conditions, only PTSD has been targeted in RCTs, with evidence supporting the use of NRT, bupropion SR, and a combination of NRT and bupropion SR in smokers with this condition (McFall et al. 2010).

Clinical trials in smokers with PTSD also provide strong support for integrating smoking cessation services within specialty PTSD treatment programs. For example, in a preliminary study, McFall and colleagues demonstrated that smokers receiving integrated treatment were several times more likely than veterans receiving standard care to refrain from smoking across the monitoring period (McFall et al. 2006). These authors extended these findings in a multicenter RCT: veterans with PTSD who smoked and who received integrated treatment were roughly twice as likely to quit smoking compared with those who received PTSD and smoking cessation services separately (McFall et al. 2010).

Smokers With Alcohol and Other Substance Use Disorders

There is compelling evidence that smokers with alcohol and other substance use disorders can quit smoking with the use of traditional smoking cessation aids and that in so doing, they do not jeopardize their sobriety (Prochaska et al. 2004). Quit rates among smokers with a past history of alcoholism treated with NRT are improved compared with quit rates in those receiving placebo (Hughes 2000), although these rates are generally lower than rates achieved in the general population (Prochaska et al. 2004). Bupropion SR has also been found to be an effective smoking cessation aid in smokers with comorbid alcoholism (Hayford et al. 1999).

Conclusion

Psychiatrists and other mental health professionals are uniquely poised to intervene in tobacco dependence. By challenging myths that interfered with our early adoption of evidence-based smoking cessation treatments, psychiatrists can have a major impact on helping patients to quit. In doing so, not only will we decrease the morbidity and mortality associated with smoking but we will also improve our patients' mental health and overall well-being.

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CHAPTER 56

Individual Therapy for Substance Use Disorders

George E. Woody, M.D.

Individual therapy for persons with substance use disorders takes many forms, but among these, drug counseling is most commonly used. Here, the focus is on individual drug counseling. I begin with comments on how it differs from psychotherapy, then discuss general treatment principles and the importance of the therapist-patient relationship, and end a review of treatment outcome findings.

Psychotherapy and Counseling: Similarities and Differences

Psychotherapy focuses on changing behaviors, thoughts, and feelings that appear to promote, maintain, or occur in association with the addiction. The areas of focus are mainly a function of the type of therapy used by the therapist. All psychotherapies are delivered in the context of a supportive, nonjudgmental relationship, and their focus is on the relationship between drug use and intrapsychic or interpersonal processes rather than external events. Psychotherapy usually requires several years of training and is typically done by persons at the master's or doctoral level.

Drug counseling is less focused on identifying and changing psychological or interpersonal processes and places more emphasis on behaviors, external events, and current life problems that are directly related to drug use and its consequences (Mercer and Woody 1999). Counselors monitor urine and breathalyzer test results; are often the first to encounter and respond to social, medical, or psychiatric emergencies; encourage abstinence from abusable substances and compliance with programmatic rules; and provide such services as referrals for jobs, housing, medical services, or legal aid. Counseling directly addresses addictive behavior, often using the language and concepts of the Twelve-Step program developed by Alcoholics Anonymous and

sometimes using confrontation of addictive behaviors.

Counseling can overlap with cognitive therapy in its emphasis on "triggers" or high-risk situations and how to avoid or manage them as part of relapse prevention efforts. In this way, counseling and psychotherapy have become somewhat merged in practice; however, the emphasis of counseling is more directly focused on encouraging cessation of drug use, providing services, and identifying and modifying external events that contribute to drug use as compared with the more internal intrapsychic focus of psychotherapy. Regardless of their orientation, effective therapists and counselors often use similar interpersonal skills, including active listening, empathy, and providing support and advice. Beyond these skills, however, there are strategies and tools associated with counseling and psychotherapy that can be readily identified by independent observers (Barber et al. 2004).

General Principles

Twelve-Step and Other Self-Help Programs

Participation in 12-step programs such as the ones at Alcoholics Anonymous and Narcotics Anonymous is highly recommended by most addiction treatment programs. Key aspects of the 12-step philosophy are the fact that programs are open to anyone who wants to stop alcohol or drug use; the belief that addiction is a disease that damages the whole person—physically, mentally, and spiritually—and that recovery must address all those domains; the fact that healing or recovery comes from connecting to something larger than oneself; the paradox that one must surrender in order to be empowered to attain sobriety; the idea that interpersonal support is critical for recovery; and the belief that recovery is a lifelong process. Research has shown that the frequency of attendance and participation in 12-step meetings is positively associated with outcome (Etheridge et al. 1999; Weiss et al. 1996) and that this participation enhances outcomes when combined with counseling or psychotherapy (Fiorentine and Hillhouse 2000).

Treatment Settings

Counseling has typically been done in programs that are separated from mainstream health care. However, the Affordable Care Act (ACA) places increased emphasis on integrating substance abuse treatment and primary health care and is likely to increase the degree to which identification and treatment of substance use disorders occurs within those settings. Treatment in any setting has varied greatly in such basic aspects as philosophy; availability of psychiatric, medical, and social services; processes used to minimize behavioral problems; type and level of illicit drug use permitted or treated; use of psychotropic drugs; educational background of staff; and types of patients. It will be interesting to see if the ACA expands treatment services while also reducing their variability.

Integration of Individual Therapy With Other Aspects of Treatment

Counseling and other individual therapies probably have the best chance to work when used with random urine testing done at intervals specific to the stage in treatment (e.g., more frequent testing until abstinence is established) and in a setting where psychiatric, medical, and social problems can be addressed, either on site or by referral. Urine testing en-

courages honesty but may also encourage patients to evade detection and thus should involve observation or other types of validity checks, such as pH, creatinine level, and temperature testing. Saliva and hair testing may be even more useful because they avoid the more intrusive aspects of urine testing.

Family problems often contribute to the onset or maintenance of substance use disorders. Engaging family members or significant others in the treatment process can be helpful on many levels, including explaining and obtaining support for the treatment process, addressing family interactions that might undermine treatment, or enlisting family members to supervise medication adherence.

Therapy Frequency and Helping Relationship

The "dosage" of counseling or psychotherapy necessary to produce meaningful improvement is unclear. In research with patients maintained on methadone, counseling and psychotherapy have typically been offered once a week, but patients have attended, on average, once every 1.5–2.0 weeks (Woody et al. 1983, 1985, 1995). However, patients were receiving methadone, so the overall intensity of therapy was high. A study evaluating the optimal frequency of drug counseling with or without additional services for methadone patients found that outcomes were better with 30–45 minutes of weekly counseling versus brief monthly counseling. Outcomes were further improved when weekly counseling was supplemented with other medical and psychiatric services on site (McLellan et al. 1993); however, about 30% of the patients in this study did well with brief monthly counseling and methadone.

For cocaine use disorders, Hoffman et al. (1991) found that intensive day treatment with group or individual counseling produced better outcomes than weekly therapy. Another study compared twice-weekly, once-weekly, and biweekly counseling over 12 weeks and found that improvement was equal across all groups and was not related to counseling frequency (Covi et al. 2002). Similarly, in the National Institute on Drug Abuse (NIDA) Cocaine/Psychotherapy Study, there was only a weak relationship between frequency of counseling and outcome (Crits-Christoph et al. 1999).

For cannabis use disorders, Stephens et al. (1994) found substantial and equal reductions in frequency of marijuana use and associated problems at 12 months posttreatment among 212 men (161) and women (51) who were randomly assigned to a relapse prevention group or a social support group. In a later study, Stephens et al. (2000) randomly assigned 291 patients seeking treatment for marijuana-related problems to a 14-session cognitive-behavioral group treatment focused on relapse prevention, a brief 2-session individual motivational interviewing treatment, or a 4-month delayed treatment control condition. Results were that participants in the active treatments showed significantly greater improvement than the delayed treatment at 4-month follow-up with no significant differences between the two active treatments. Another study compared two sessions of motivational enhancement therapy (MET); nine sessions of a multicomponent therapy that included MET, cognitive-behavioral therapy (CBT), and case management; and a delayed-treatment control condition. The best results were obtained by the nine-session multicomponent treatment followed by the two-session MET, each of which did bet-

ter than the wait-list control (Marijuana Treatment Project Research Group 2004). For alcohol use disorders, once-monthly MET had comparable drinking outcomes to more intensive cognitive-behavioral and 12-step facilitation therapies (Project MATCH Research Group 1997).

These data suggest that the intensity of psychotherapy or counseling needed to produce a treatment effect may vary with the drug, the patient's psychiatric problems, and whether or not an effective pharmacotherapy is used. The dropout rate in treatment for amphetamine, cocaine, and cannabis use disorders is typically high, and efforts are under way to find effective medications that help keep patients in so that counseling or psychotherapy can be provided.

Therapeutic Alliance

Therapist qualities such as overall adjustment, skill, and interest in helping patients have long been shown to have positive effects on outcome (Luborsky et al. 1985, 1986). However, research has not identified specific types of therapists who are more (or less) effective in treating addiction (Crits-Christoph et al. 1990). Studies have shown that a therapist who is able to establish a positive connection with the patient at the beginning of treatment and is perceived by the patient as helpful is more likely to achieve more treatment retention and reductions in drug use (Luborsky et al. 1985). This relationship between a positive alliance and outcome appears to hold across different modalities and disorders (Connors et al. 1997; Horvath and Symonds 1991). It has been theorized that therapists' reactions to patients ("countertransference") are important determinants of the helping alliance and that therapists should be especially cognizant of the potential for substance-abusing patients to elicit intense or negative responses that can have a negative impact on outcome (Imhof 1991).

Treatment Outcome

Opioid Use Disorder

Counseling or psychotherapy in the absence of methadone, buprenorphine, or naltrexone is ineffective for all but a very few patients who are addicted to opioids (Mayet et al. 2004). In a study conducted at a U.S. Department of Veterans Affairs methadone maintenance program, drug counseling alone was compared with counseling plus supportive-expressive psychotherapy or CBT. Patients who received psychotherapy improved more than those with counseling alone, but the benefits were mainly due to improvements in patients with high levels of psychiatric symptoms; patients with low symptom levels improved as much with counseling alone as with extra psychotherapy (Woody et al. 1983, 1985). These findings were confirmed in community-based programs (Woody et al. 1995); however, a similarly designed study compared interpersonal therapy with counseling and did not find a psychotherapy effect (Rounsaville et al. 1983). Reasons for the differences may have been low enrollment; the degree to which therapists were integrated into treatment programs; and suspending from methadone maintenance patients who did not stop drug use, thus leaving relatively little variability in patterns of drug use (Woody 2003). A recent study of CBT in primary care–based buprenorphine treatment found no evidence that it resulted in better outcomes than medically focused physician management (Fiellin et al. 2012).

Cocaine Use Disorder

The largest study of psychotherapy and counseling for cocaine dependence was the NIDA Collaborative Cocaine Treatment Study (Crits-Christoph et al. 1999), in which 487 patients were randomly assigned to receive one of four psychosocial treatments in outpatient settings: 1) cognitive therapy plus group drug counseling, 2) supportive-expressive therapy plus group drug counseling, 3) individual drug counseling plus group drug counseling, and 4) group drug counseling alone. Treatment was intensive, with 36 possible individual and 24 possible group sessions over 6 months. At admission to the study, patients were using cocaine (mainly crack) 10 days per month on average. Although all groups showed reductions in cocaine use (average of 10 days/month at baseline to 1 day/month at 6 months), patients receiving individual and group drug counseling reduced cocaine use to a greater degree than those in the other treatment groups. Patients with higher levels of psychiatric symptoms had poorer outcomes across all treatments, but in these studies, unlike some of the methadone studies, psychotherapy did not provide additional benefits to patients with higher levels of psychiatric impairment.

In other studies, behavioral interventions such as community reinforcement (Higgins et al. 1993), voucher-based reinforcement (Silverman et al. 1996), and reinforcement for completing treatment plan–related tasks (Iguchi et al. 1997) had positive effects. Rawson et al. (2002) compared behavioral interventions with psychotherapy and counseling in patients with cocaine use disorders who were maintained on methadone, and contingency management or CBT produced more improvement than drug counseling.

Another study compared relapse prevention plus desipramine, clinical management plus desipramine, relapse prevention plus placebo, and clinical management plus placebo. All groups improved, but there were no main effects with pharmacotherapy or psychotherapy (Carroll et al. 1994). However, relapse prevention was associated with better outcomes than was clinical management in patients with higher levels of cocaine use, and further analyses suggested that desipramine was effective in reducing depression but not in reducing cocaine use (Carroll et al. 1995).

In summary, the largest of these studies (Crits-Christoph et al. 1999) found that the combination of individual and group counseling is as or more effective than psychotherapy in patients with cocaine use disorders. The findings of Higgins et al. (1993) showed an advantage for CBT compared with counseling; those of Carroll et al. (1994, 1995) suggested a benefit from relapse prevention therapy for patients with more severe cocaine use or depression. The most reassuring aspect of these studies is that they all showed substantial reductions in cocaine use.

Alcohol Use Disorder

Project MATCH (Matching Alcoholism Treatments to Client Heterogeneity) compared CBT, 12-step facilitation therapy (Nowinski et al. 1992), and motivational enhancement therapy (Miller et al. 1992) for treating alcohol use disorders. With all treatments, patients decreased alcohol use significantly and maintained improvement 1 year after treatment. There was no difference in outcome between treatments, and higher levels of psychiatric symptoms were associated with worse outcome. As in the NIDA Collaborative Cocaine Treatment Study, the re-

sults from 12-step program–oriented drug counseling compared favorably to those associated with psychotherapy.

Cannabis Use Disorder

Grenyer and Solowij (2006) compared a one-session intervention and a modification of supportive-expressive psychotherapy. At 16 weeks the supportive-expressive psychotherapy group showed significantly greater decreases in marijuana use, depression, and anxiety and greater increases in psychological health than did the brief intervention group. Other studies compared one or more psychotherapies with contingency management or other treatments for cannabis use disorder but not with drug counseling. A review of many individual therapy studies showed that patients improved but that outcomes were generally similar across therapies (Nordstrom and Levin 2007).

Comorbid Psychiatric Disorders

Mills et al. (2012) conducted a study of a therapy that combined MET and CBT for substance use with exposure therapy for PTSD for 103 patients who had both disorders. The most common substance use diagnosis was polysubstance dependence (as per DSM-IV; American Psychiatric Association 1994) involving benzodiazepines, cannabis, and alcohol. Significant reductions in PTSD and the severity of substance use occurred in the experimental and usual treatment control groups, with greater reductions in PTSD severity in patients who were randomly assigned to the experimental condition.

Personality disorders are common among individuals with substance use disorders and are notoriously difficult to treat. Ball et al. (2011) conducted a randomized comparison of dual focus schema therapy with individual drug counseling for 105 patients with or without personality disorders who had been referred to residential treatment from criminal justice or child protection agencies. Lifetime substance use diagnoses included alcohol (41%), cocaine (31%), cannabis (31%), and opioids (20%). Patients who received individual drug counseling had more improvement than those in dual-focus therapy.

Treatment Implications

Although the relative benefits of psychotherapy and counseling varied, many studies agreed that both can be effective and, moreover, that counseling and psychotherapy are necessary components of substance use disorder treatment. The intensity of therapy necessary to produce positive effects seems to vary according to the type of addiction, with cocaine and opioid addiction requiring the most intensive treatment, especially at the beginning of therapy. In the case of treatment for opioid addiction, methadone, buprenorphine-naloxone, or naltrexone is essential for psychotherapy or counseling to be helpful because dropout rates are very high in the absence of medication. Two of the three studies done with patients maintained on methadone indicate that psychotherapy is useful, mainly for patients with high levels of psychiatric symptoms. Studies of patients with alcohol or cocaine use disorders have not found a clear advantage of psychotherapy over counseling, but, unlike with persons addicted to opioids, they have found that outpatient "drug-free" psychosocial treatment can be effective.

Interestingly, most studies have failed to show that one kind of psychotherapy is superior to any other for the treatment of addiction or for other psychiatric disor-

ders. There is much interest in combining psychological and pharmacological treatments and an emerging interest in bringing addiction treatment into primary care, HIV, and general psychiatric treatment settings. It is also important to recognize the high value of participation in 12-step and other self-help groups. Consistent with the ideas of Alcoholics Anonymous, it is best to view treatment and recovery as a process that needs to continue over an extended period of time.

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CHAPTER 57

Cognitive, Behavioral, and Motivational Therapies for Substance Use Disorders

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Drug and alcohol use disorders have affected approximately 30% of American adults at some point during their lifetime (Compton et al. 2007; Hasin et al. 2007). Of those reporting a lifetime substance use disorder, approximately 39% have sought treatment. These individuals are most likely to seek the assistance of health care professionals (including physicians and counselors), with 12-step programs being the second most relied on support system (Compton et al. 2007; Hasin et al. 2007).

Psychosocial interventions remain the cornerstone of substance abuse treatment services. There are more than 250 evidence-based programs and practices listed in the Substance Abuse and Mental Health Services Administration's national registry for the prevention and treatment of mental health and substance use disorders (see Table 57–1 for URL). Further, the National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism have outlined the treatment options available to substance users and their families as well as standardized protocols that provide session-to-session guidance for practitioners (National Institute on Alcohol Abuse and Alcoholism 2007; National Institute on Drug Abuse 2009) (see Table 57–1). However, behavior change is an incremental process that may involve both specific and varied strategies (Prochaska et al. 1992). Prochaska and DiClemente's (1983) transtheoretical model of intentional behavior change offers a useful heuristic for both gauging an individual's position throughout the change process and guiding clinical strategies that can be implemented as individuals

move from a perception of having no problem (precontemplation) to the identification of problems and having mixed feelings about change (contemplation) to the long-term alteration of behavioral patterns (maintenance) (see Table 57–2).

In this chapter we aim to provide a selective overview of different support services and empirically based psychosocial treatment strategies that can assist clinicians in helping individuals address the motivational, cognitive, and behavioral dimensions associated with changing problematic substance use, and resources are presented at the end of the chapter. A treatment episode may involve the selective use of only a few of the highlighted strategies or a more comprehensive implementation of several treatment protocols.

Building Motivation for Treatment Entry

A majority of individuals with substance use disorders do not seek treatment (Compton et al. 2007; Hasin et al. 2007), and among those who do, attrition rates are notable (Dutra et al. 2008). Clinicians may wrestle with motivational issues during all phases of treatment. Pretreatment motivational issues are often presented by concerned family members seeking advice on how to help loved ones who are not interested in seeking help. Support services and treatment-based options can be useful at this juncture. Nar-Anon and Al-Anon are community-based support groups for relatives and friends of individuals struggling with drug or alcohol use problems, respectively (see Table 57–3). On the basis of 12-step principles and traditions, both organizations focus on helping family members obtain a better understanding of the addiction process and develop a readily accessible support network by interacting with others sharing similar experiences. They are not focused on directly influencing the behavior of the substance user.

Providing family members with skills that can increase the probability of the substance user entering treatment is an alternative approach for addressing pretreatment motivational issues. The Johnson Institute's planned family intervention (Johnson 1986) is a structured protocol implemented by family members under the guidance of a trained professional. Family members are educated about addiction and collaborate on an individualized treatment plan. This is followed by a planned meeting in which the substance user is given detailed feedback on how his or her substance use has affected others and the contingencies for treatment entry and nonentry. The goal of the intervention is to motivate the substance user to enter treatment in the context of a direct but supportive interaction. Planned family interventions have demonstrated significant efficacy when family members accurately implement the intervention (Miller et al. 1999), although less than half of those families who complete the training follow through (Liepman et al. 1989).

Community reinforcement approach and family training (CRAFT; Smith and Meyers 2004) is a nonconfrontational therapy program for concerned family members or friends of individuals with substance use problems who refuse to seek treatment. The program has three goals: 1) influence the substance user to seek treatment, 2) reduce the amount of substances used by the individual until he or she enters treatment, and 3) help concerned family members make other life changes to support and improve their own psychological functioning. Family members receive training in identifying the antecedents and consequences of an

TABLE 57–1. Treatment resources for the practicing clinician

	Material	URL
Information		
SAMHSA's Registry of Evidence-Based Programs and Practices	Descriptions and contact information for treatments	http://www.nrepp.samhsa.gov/ViewAll.aspx
Brief therapies for substance abuse	Booklet: "Treatment Improvement Protocol"	http://www.ncbi.nlm.nih.gov/books/NBK64947/
Principles of drug addiction	Information booklets	http://www.drugabuse.gov/nidamed/tool-resources-your-practice/treatment-information
National Institute on Drug Abuse archives	Library of downloadable booklets and manuals	http://archives.drugabuse.gov/pubs/index.html
Specific treatment protocols		
Relapse prevention therapy (NIDA)	Treatment manual	http://archives.drugabuse.gov/TXManuals/CBT/CBT1.html
Community reinforcement approach (NIDA)	Treatment manual	http://archives.drugabuse.gov/TXManuals/CRA/CRA1.html
Individual drug counseling (NIDA)	Treatment manual	http://archives.drugabuse.gov/TXManuals/IDCA/IDCA1.html
Brief intervention for marijuana dependence	Treatment manual	http://store.samhsa.gov/product/Brief-Counseling-for-Marijuana-Dependence-A-Manual-for-Treating-Adults/SMA12-4211
Motivational interviewing	Treatment manuals and guides	http://www.motivationalinterview.org/quick_links/manuals.html http://www.ncbi.nlm.nih.gov/books/NBK64967/
MI organizations, training		http://www.motivationalinterviewing.org

TABLE 57–1. Treatment resources for the practicing clinician *(continued)*

	Material	URL
Specific treatment protocols *(continued)*		
ACT	Training and literature resources	http://contextualpsychology.org/act
MBRP	Training resources and manual	http://www.mindfulrp.com
National Institute on Alcohol Abuse and Alcoholism library (includes coping skills, motivational enhancement, and 12-step facilitation programs)	Treatment manuals and information brochures	http://www.niaaa.nih.gov/publications/clinical-guides-and-manuals
Treatment Research Institute	Tools for implementing empirically based treatments	http://triweb.tresearch.org/index.php/tools/for-clinicians/roadmap-toolkit/

Note. All Web sites accessed December 4, 2012.
ACT=acceptance and commitment therapy, MBRP=mindfulness-based relapse prevention; CRAFT=community reinforcement approach and family training; MI=motivational interviewing; NIDA=National Institute on Drug Abuse; SAMHSA=Substance Abuse and Mental Health Services Administration.

TABLE 57–2. Clinical strategies as guided by Prochaska and DiClemente's Stages of Change Model

Stage of change	Clinical characteristics	Intervention goal	Intervention(s)
Precontemplation	Unawareness of problem behavior Unwillingness and/or discouragement when it comes to changing a behavior	Raise awareness of the problem behavior Increase motivation to consider change Provide skills and support to members of the individual's social network	CRAFT, Johnson Institute intervention, family support (Al-Anon, Nar-Anon)
Contemplation	Acknowledgment of a problem Struggle to reconcile the pros and cons of change	Help the individual tip the balance toward change Create a context for increasing a commitment to change	Motivational interviewing, contingency management
Preparation	Individual appears ready or on the verge of making change Strong verbal commitment to take action to change	Help develop a change plan Explore the potential barriers to change and outline steps to overcome them	Motivational interviewing, contingency management, goal-setting exercises in skills-based programs (ACT, RPT, CRA)
Action	Overt modification of behavior Increase in ambivalence in the face of setbacks	Build self-efficacy Problem solve or modify change plan as needed in response to successful lifestyle change or setbacks	Motivational interviewing (as needed), skills-based interventions
Maintenance	Successful behavior change Probability of the old, undesired behavior to return	Build social and contextual supports to help maintain new behavioral patterns Build a broad and flexible behavioral repertoire to meet the challenges of a new lifestyle Review skills to decrease the probability that	Selected modules of skills-based interventions, facilitation of building social support networks (e.g., AA, NA, SMART recovery)

TABLE 57–3. Resources for the consumer

Intervention	Format	Title or URL
CRAFT	Book	*Get Your Loved One Sober: Alternatives to Nagging, Pleading, and Threatening* (Meyers and Wolfe 2004).
Johnson Institute intervention	Book	*How to Help Someone Who Doesn't Want Help* (Johnson 1986)
RPT and coping skills	Workbook	*Overcoming Your Alcohol or Drug Problem: Effective Recovery Strategies Workbook* (Daley and Marlatt 2006)
ACT-based treatments	Workbooks	*The Wisdom to Know the Difference: An Acceptance and Commitment Therapy Workbook for Overcoming Substance Abuse* (Wilson and DuFrene 2012) *Get Out of Your Mind and Into Your Life: The New Acceptance and Commitment Therapy* (Hayes and Smith 2005).
Self-help organizations	Descriptions, meeting information, and pertinent literature	http://www.al-anon.alateen.org/home (Al-Anon) http://www.nar-anon.org/naranon/ (Nar-Anon) http://www.aa.org (Alcoholics Anonymous) http://www.na.org (Narcotics Anonymous) http://www.smartrecovery.org (SMART Recovery)

Note. All Web sites accessed December 4, 2012.
ACT=acceptance and commitment therapy; CRAFT=community reinforcement approach and family training; RPT=relapse prevention therapy.

individual's substance use and use this knowledge to increase sober behavior. Training also focuses on strengthening the communication skills of family members, addressing domestic violence, and helping significant others enrich their own lives. CRAFT has demonstrated significant efficacy in promoting treatment entry among drug and alcohol users (69%–80%; Meyers et al. 2002; Miller et al. 1999).

Enhancing Motivation During Treatment

Ambivalence can be a normal part of the change process and may define a client's motivational state for a significant period of time. Thus, addressing motivational issues may be a central theme during the treatment process. Treatment engagement is influenced more strongly by the interpersonal and structural parameters of an intervention than the specific characteristics of patients (Miller 1985). Confrontational, less collaborative, and more directive counseling styles can negatively impact the efficacy of psychosocial interventions (Najavits and Strupp 1994), including treatments for substance use disorders (Miller et al. 1993; Moyers and Miller 2013). Alternatively, a collaborative working relationship and strong therapeutic alliance can positively affect treatment outcome (Crits-Christoph et al. 2011).

Motivational interviewing (MI) is a client-centered counseling style for addressing the common problem of ambivalence about change (Miller and Rollnick 2013). Clinicians counseling within an MI framework use a set of microskills (i.e., open questions, affirming, reflective listening, and summarizing) to increase a client's language relating to change and commitment. Importantly, MI is conducted as a partnership in which the clinician brings a nonjudgmental stance that actively promotes the welfare of the person, respects his or her autonomy throughout the change process, actively seeks to acknowledge his or her strengths, and educes the argument for change from his or her own experiences and perspective (i.e., MI spirit). Skillfully interlacing microskills and the MI spirit defines the proficient and successful implementation of an MI approach. MI has demonstrated efficacy for treating alcohol and drug use disorders as well as other health-related behaviors (Hettema et al. 2005) across a range of treatment formats (Rollnick et al. 2008; Steinberg et al. 2005).

Structuring the clinical environment so treatment-consistent behavior is objectively verified and linked to well-defined and predictable responses has been particularly effective for increasing treatment engagement and reducing substance use (Higgins and Silverman 1999). Contingency management (CM) is the overarching term for a class of treatments that provide tangible outcomes for substance-free urine samples and/or the completion of treatment plan activities. The common process underlying all CM-based interventions is the differential reinforcement of non-drug-use behavior to strengthen a behavioral repertoire that promotes a healthier and more valued lifestyle. Employing a formal CM system provides a higher probability that the incremental steps of change are recognized and positively reinforced, thus increasing motivation and treatment engagement. These procedures can help mitigate the potentially pernicious effects of an extended history of criticism and punishment that may obscure the relatively small but impor-

tant successes occurring during the early phases of a treatment episode. The objective verification of treatment successes (e.g., substance-free urine) is couched in a "catching people doing right" framework that can validate clients' improvement and build the confidence and trust of members in their social network.

CM principles have been utilized in voucher-based incentive programs (e.g., earning increased monetary rewards as the period of abstinence increases); prize bowl strategies that offer a relatively lower cost CM structure (i.e., probabilistic winnings from a prize bowl), which may facilitate their adoption in community-based settings; take-home medication schedules utilized in methadone maintenance clinics; assisted housing arrangements; and earning access to work environments (Higgins et al. 2008; Petry 2012). Office-based CM procedures can include the earning back of initial financial deposits for treatment plan adherence. Although CM-based treatment protocols have demonstrated some of the most robust treatment retention rates and outcomes (Dutra et al. 2008), the strong effect tends to dissipate after the CM structure is removed. Thus, treatment gains may be more likely to be retained when augmented with other treatment strategies.

Skills-Based Interventions: First- and Second-Generation Behavioral Approaches

Historical accounts of behavior therapy have outlined three waves of treatment development (Hayes 2004). A majority of cognitive-behavioral interventions for substance use disorders are grounded in traditional learning theory principles of classical and operant conditioning (Wave 1) and/or cognitive formulations of psychopathology (Wave 2).

Classical conditioning interventions for drug dependence parallel the procedures employed during exposure-based treatments for other psychological disorders (e.g., phobias). Cue reactivity (i.e., heart rate, skin temperature, and cognitive responses) predicts relapse among substance users. Thus, exposure-based treatments that present drug-related stimuli (pictures, the actual presentation of paraphernalia, visual imagery) while individuals are asked to monitor their cognitive and physiological responding in the presence of these cues have been developed (e.g., O'Brien et al. 1990). Exposure-based treatments have demonstrated efficacy in reducing the physiological and cognitive responses to drug cues, although the effect on substance use and abstinence has been less consistent. Some studies suggest that blending exposure sessions with skills-based interventions can bolster the effects of both treatment strategies (Monti et al. 2001; Rohsenow and Monti 2012). It has also been argued that these treatment strategies may be improved if they are more strongly anchored to the empirical findings and theoretical formulations of extinction-based learning (see Conklin and Tiffany 2002 for detailed suggestions).

Skills-based treatments for substance use disorders share the perspective that substance use is a learned behavior that serves a range of functions for a given individual (e.g., coping response and social enhancement). Marlatt and Gordon's (1985) influential publication conceptualized the process of addiction and change in terms of the social and psychological factors influencing the transition from substance use to abstinence. Therapies aligned with this conceptual perspective address the social, psychological, and behavioral factors that contribute to contin-

ued substance use. They often utilize the cognitive and behavioral strategies underlying the treatment of other behavioral and psychological disorders. Recognize, Avoid, Cope, and Evaluate (RACE; Carroll 1998) serves as a useful container for the types of skills introduced during this course of treatment. Specifically, interventions employ self-monitoring exercises to help identify the environmental and subjective contexts in which substance use is likely to occur (Recognize). Further, treatments develop behavioral strategies to minimize contact with high-risk situations (Avoid) and build cognitive and behavioral techniques for responding to cravings, thoughts about substance use, and high-risk situations (Cope). These treatments also help individuals analyze the decision-making process to minimize the influence of more immediate reinforcement, develop cognitive strategies to promote the attainment of longer-term goals, practice behavioral strategies to reduce the influence of socially mediated threats to abstinence, and outline explicit plans for escaping situations that threaten an individual's goal of abstinence. The overall utility of each of the strategies implemented during treatment is continuously analyzed and modified in the service of maintaining a client's abstinence (Evaluate).

A defining characteristic of skills-based treatments is the active engagement of skill building during a counseling session as well as the use of formal procedures to promote the implementation of these skills in the client's natural ecology. The use of in-session role playing and rehearsal, such as learning to refuse the offer to use drugs, serves to introduce the pertinent skills and help expand the client's behavioral repertoire. Out-of-session exercises are created to facilitate the generalization of the skills to other situations. Further, relapse is conceptualized as a process rather than a dichotomous end state defined as having relapsed or not. Thus, clients are educated about the decision processes that can influence the transition from an initial use episode (i.e., lapse) to the reinstatement of a broader and more persistent behavioral pattern (i.e., relapse). Skills-based interventions encompass a diverse set of intervention strategies differing in the degree a particular treatment emphasizes cognitive, behavioral, or environmental management techniques. For example, relapse prevention therapy (Carroll 1998; Marlatt and Gordon 1985) emphasizes both behavior and cognitive skills building. A community reinforcement approach, while emphasizing similar skill building, more formally addresses the importance of environmental reinforcers (Budney and Higgins 1998; Meyers and Smith 1995). Cognitive therapy (Beck et al. 1993) places stronger emphasis on targeting an individual's underlying belief structure that results in continued substance use.

Skills-based interventions have demonstrated significant efficacy in treating alcohol, opioid, stimulant, and cannabis use disorders relative to traditional counseling services and non-substance-specific psychotherapies in 12–24 week treatment studies (Carroll 1996; Dutra et al. 2008). Direct comparisons among different skills-based interventions have yet to identify a single superior skills-based protocol across all substances. However, evidence specifically supports the use of well-defined, theoretically driven, and structured interventions for treating substance dependence relative to other counseling approaches (Carroll and Rounsaville 2010). Further, recent developments in computer-assisted therapy technologies have expanded the accessibility of skills-based interventions to a

wider range of clinical contexts such as CBT4CBT (Carroll et al. 2008) and Therapeutic Educational System (Bickel et al. 2008). Clinical trials indicate that computer-assisted protocols can increase the efficacy of supportive counseling programs. They can serve as an extension of therapy by providing a consistent context for skill development that may give counselors the flexibility to focus on other important issues as needed. It is important to note that individuals with relatively lower cognitive functioning are at an increased risk for early treatment dropout in skills-based interventions (Aharonovich et al. 2006). Thus, the use of motivation-building strategies, variations in treatment pacing and presentation (Brooks et al. 2012), and computer-assisted therapies may help mitigate the deleterious effects of cognitive impairment during treatment.

Third-Generation Behavior Therapies

Third-generation behavior therapies for substance use disorders have expanded behavioral formulations of maladaptive behavior and introduced a range of different therapeutic strategies that can be utilized to address clinical problems. This class of treatments is characterized by their emphasis on adopting an openness and acceptance toward the psychological and emotional responses experienced during the change process. There is less emphasis on changing the content of one's thoughts or directly eliminating unwanted emotional and physiological responses. Therapeutic exercises and behavioral skills are introduced in the service of developing a more flexible cognitive and behavioral repertoire that can help facilitate important lifestyle changes. Examples of these treatments include dialectical behavioral therapy (Linehan 1993), mindfulness-based cognitive-behavioral therapy (Segal et al. 2012), mindfulness-based relapse prevention (Bowen et al. 2011), and acceptance and commitment therapy (Hayes et al. 2012). Several of these treatment programs have developed specific protocols for assisting individuals with substance use problems (e.g., Bowen et al. 2011; Hayes et al. 2004; Linehan et al. 2002).

Mindfulness-based relapse prevention (MBRP) is a structured outpatient treatment protocol that utilizes mindfulness medication practices in conjunction with skills-based training to help individuals manage or prevent relapse episodes (Bowen et al. 2011). The relapse prevention skills are similar to those introduced in other coping skill protocols (e.g., identifying triggers and balancing lifestyle). However, MBRP introduces formal sessions and practices that help individuals take an observing stance toward their internal responses (e.g., drug urges or stress) without automatically engaging in substance use. Sessions are structured to help individuals adopt an accepting stance toward experiencing unwanted emotions, sensations, or thoughts. They are guided to relate to their thoughts differently (e.g., not always buying into the content of their thoughts) and engage in formal exercises to increase their skill in mindful meditation practices. These practices are introduced with the goals of undermining the automaticity of substance use, disrupting the relapse cycle, and fostering a healthier lifestyle. MBRP has demonstrated efficacy in treating alcohol use disorders (Bowen et al. 2006, 2009), and evidence suggests that it may be a useful intervention for other substance use disorders (Dakwar et al. 2011).

Acceptance and commitment therapy (ACT; Hayes et al. 2012) is a third-gener-

ation psychotherapy based on a comprehensive behavioral formulation of language and cognition (i.e., relational frame theory) (Hayes 2004). ACT incorporates some first- and second-generation therapeutic strategies (e.g., behavioral assignments and skills acquisition) in addition to mindfulness-based practices and other psychological processes to undermine an individual's overarching strategy of avoiding emotional and cognitive experiences at the expense of living a more valued life. ACT treatment protocols attempt to strengthen six core processes (acceptance, cognitive defusion, being present, a perspective of self-as-context, clarifying valued directions, and developing committed action) in order to facilitate greater psychological flexibility. Thus, throughout this process the automaticity of overlearned substance use responses is diminished, which provides opportunities for other psychological and behavioral responses to occur. ACT protocols have been developed and tested among substance-using populations and have been demonstrated to be more efficacious than treatment-as-usual comparisons and as effective as other structured treatment protocols (Bricker et al. 2010; Twohig et al. 2007). Clinician-based treatment protocols and self-help workbooks are available for general behavioral (Hayes and Smith 2005) and substance abuse problems (Wilson and DuFrene 2012) (Table 57–3).

Interventions Informed by Cognitive Science

Research demonstrating memory retrieval biases, attentional biases, and information-processing biases among substance users has led to other developments in the treatment of substance use disorders (Carpenter et al. 2006; Field and Cox 2008). These treatment approaches fit within the broader category of cognitive bias modification programs. Cognitive bias modification is characterized by a set of structured procedures that target the specific cognitive processing styles believed to promote maladaptive emotional and behavioral responding (Hertel and Mathews 2011). The modification procedures are operationalized by a systematic set of practice exercises that attempt to train alternative cognitive processing styles. It is hypothesized that directly addressing the biased cognitive processing promoting substance use can yield a more powerful strategy for interrupting the cognitive and behavioral sequences that underlie the persistent nature of drug dependence.

Cognitive processing modification programs have been developed to alter attentional biases (Schoenmakers et al. 2010) and automatic action tendencies (Wiers et al. 2011) among patients with alcohol dependence and to improve working memory, an executive functioning process associated with improved treatment performance (Houben et al. 2011) and other cognitive processes associated with substance use disorders (Bickel et al. 2011). Although cognitive bias modification procedures and cognitive training have been applied to a variety of other psychiatric populations, their application in treating substance dependence problems is a relatively new intervention strategy. Thus, although initial studies (e.g., Schoenmakers et al. 2010) have been promising, the use of these cognitive training strategies awaits continued development and empirical validation. The outcomes of these ongoing novel applications offer the promise of both expanding the range of intervention strategies available to clinicians and increasing the efficacy of the well-delineated and empirically validated treat-

ment approaches already being implemented in clinical settings.

Conclusion

Psychosocial interventions provide effective strategies for guiding transitions from chronic drug use to a drug-free lifestyle. However, different intervention techniques may be needed to address the full range of motivational, cognitive, and behavioral factors associated with successful treatment outcomes. Thus, developing a flexible and broad clinical repertoire may offer a clinician the most practical and effective framework for addressing substance use disorders. In this chapter we provided an overview of different treatment strategies and resources available to both the clinician and the clients who are seeking help for substance abuse problems. The implementation of these treatment strategies offers a robust empirically based platform for assisting individuals and their families throughout the process of change.

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CHAPTER 58

Group Therapy for Substance Use Disorders

Arnold M. Washton, Ph.D.

In this chapter I provide a brief overview of the role, efficacy, advantages, and disadvantages of group therapy in the treatment of substance use disorders. I describe the complementary roles of group therapy and mutual self-help groups, the four most commonly used group therapy approaches, and important considerations in setting up and conducting substance abuse treatment groups. Additional information on these and other relevant topics is available from many other resources, including the references, recommended readings, and Web sites listed at the end of this chapter.

Group Therapy

Group therapy is the most prevalent modality of treatment of substance use disorders in the United States today. Moreover, it is considered by many to be the psychosocial treatment of choice for substance use disorders (Spitz and Brook 2002). The prominent role of this treatment modality can be attributed in part to the inherent goodness of fit between the clinical needs and characteristics of individuals presenting with substance use disorders and the potent combination of therapeutic forces that group therapy uniquely provides. It can also be attributed to the cost-effectiveness of group treatment. As compared with individual therapy, groups enable larger numbers of patients to be treated by fewer clinicians within the same amount of time. Even though group treatment offers both clinical and cost advantages, a combination of both group and individual therapy may produce better outcomes (Washton and Zweben 2006).

Empirical Support for Group Therapy

Despite the important role of group therapy, definitive evidence of its effectiveness in treating substance use disorders is yet to be presented. A recent review of 24 studies comparing group therapy with other treatment modalities failed to provide clear evidence to support claims of greater efficacy of group as compared

with individual treatments or that any one type of group therapy approach is more effective than others (Weiss et al. 2004). However, these researchers and others (Morgan-Lopez and Fals-Stewart 2006) have acknowledged that serious methodological, data analytic, and practical obstacles in research on group therapy severely limit the generalizability of available findings. Perhaps the strongest empirical evidence to date supporting the efficacy of group approaches comes from a large study involving 7,815 patients in 63 publicly funded outpatient addiction treatment programs. This study found higher rates of treatment completion and goal attainment in programs that provided a higher proportion of group as compared with individual sessions (Panas et al. 2003).

Complementary Roles of Group Therapy and Self-Help Groups

Self-help programs such as Alcoholics Anonymous (AA) and professionally led psychotherapy groups can be mutually beneficial and complementary. However, they are not good substitutes for one another. Although many patients find participation in self-help programs extraordinarily helpful and even life saving, a professionally led psychotherapy group offers a different kind of help. As contrasted with group therapy, self-help groups are leaderless meetings during which participants are prohibited from giving direct feedback to one another or focusing in detail on any one member's issues. These meetings are not designed or intended to address the dynamics of members' interaction with one another or to facilitate in-depth discussion regarding emotional and psychological issues—the raison d'être of group therapy.

Advantages of Group Therapy

Among the many advantages of group therapy are its ability to 1) facilitate patient engagement, retention, and compliance as a result of the bonding that develops between group members; 2) provide newcomers with a ready-made support network of peers pursuing common goals; 3) help educate group members about the fundamentals of addiction and recovery; 4) instill optimism and hope; 5) help to reduce feelings of isolation, shame, and guilt; 6) allow for sharing of useful information, ideas, and experiences; 7) provide structure, support, and accountability for change; 8) encourage and support members as they work through setbacks and other difficulties; 9) help members learn and practice coping and relapse prevention skills; and 10) provide opportunities for therapeutic confrontation and realistic feedback (Brown and Yalom 1977; Center for Substance Abuse Treatment 2005; Washton 2001).

Disadvantages of Group Therapy

Despite its many benefits, group therapy also has certain drawbacks. Whereas individual therapy affords total privacy, groups require members to reveal themselves to strangers with attendant fears about loss of anonymity and potential damage to reputations, relationships, and careers—fortunately, a rare occurrence. Because the content and pace of treatment are determined by the group as a whole and not by any one member, there are inevitably times when the group is out of step with the clinical needs of some members while in sync with the needs of others. As compared with individual sessions where the entire session is devoted to a single patient, a smaller

portion of any group session is devoted to one member.

Four Common Group Approaches

In this section, I provide an overview of four group therapy approaches that are commonly used in the treatment of substance use disorders. As the field embraces more flexible, integrative approaches (see Washton and Zweben 2006), treatment providers are more likely to combine different elements of these approaches even when their primary treatment orientation is characterized mainly by one approach.

Recovery-Focused Groups

Recovery-focused groups, which are based on the disease model of addiction and the 12-step principles of AA, have long been the traditional mainstay of treatment programs for substance use disorders (Center for Substance Abuse Treatment 2005; Nowinski et al. 1999). A primary goal of this approach is to facilitate patients' active engagement and participation in the 12-step fellowship of Alcoholics Anonymous. Essential ingredients for recovery include active involvement in 12-step programs and an ongoing commitment to maintain abstinence from all psychoactive substances (regardless of the patient's substance of choice) both during and after formal treatment.

Motivation Enhancement Groups

The focus of motivation enhancement groups based on the stages-of-change model (Center for Substance Abuse Treatment 1999; Miller and Rollnick 2013; Velasquez et al. 2001) is to engage patients in treatment, enhance their motivation and readiness for change, and support their efforts to initiate and maintain changes in substance use behavior. In contrast to traditional approaches relying heavily on confrontation of denial, motivational approaches emphasize meeting patients "where they are" in the process of change and working through ambivalence rather than confronting resistance.

Relapse Prevention Groups

Relapse prevention groups, which are based on social learning theory, incorporate a broad range of cognitive-behavioral, psychoeducational, and supportive techniques (Rawson and Obert 2002). Emphasis is placed on overcoming coping skill deficits and increasing the patient's ability to cope with various conditioned cues ("triggers") and high-risk situations that commonly precipitate relapse. It also emphasizes the importance of preventing a temporary lapse or "slip" from escalating unnecessarily into a full-blown destructive relapse.

Psychodynamic Process Groups

Psychodynamically oriented recovery groups are grounded in various psychodynamic theories (Brown and Yalom 1977; Flores 1988; Vannicelli 1992), including the widely disseminated self-medication model of addiction (Khantzian et al. 1990). A primary focus of these groups is to help patients acquire an understanding of how they have used psychoactive substances as coping tools to regulate intolerable affects that are evoked by stressful life circumstances, in-

terpersonal conflict, self-esteem problems, and/or deficits in ego functioning. These groups also help patients to identify and work through various underlying psychodynamic issues emanating from the legacy of traumas, dysfunctional relationships, family of origin issues, and the like.

Other Types of Groups

In addition to the models and approaches already mentioned, many treatment programs for substance use disorders offer phase-specific groups that focus on specific tasks and goals and help patients move from one phase of treatment to the next as they complete the requirements of each phase (Washton 2002). For example, there are pretreatment preparation groups, detoxification and stabilization groups, early recovery groups, continuing care groups, and later-stage or long-term recovery groups. There are also groups designed for specific patient populations such as adolescents, health care professionals, and patients with co-occurring psychiatric disorders, including mood disorders, eating disorders, posttraumatic stress disorders, and various personality disorders (Weiss and Connery 2011). Only recently have treatment options expanded to include harm reduction and moderation groups for patients seeking alternatives to abstinence-focused treatment (Little 2002).

Clinical and Practical Considerations

Group therapy for substance use disorders has historically been available only in specialized treatment programs. By contrast, substance use treatment groups have not been readily available in office-based practice settings, although this situation has been changing in recent years as more office-based psychiatrists, psychologists, and other mental health practitioners have become proficient in treating substance use disorders (Washton and Zweben 2006). Regardless of treatment setting, important considerations in setting up and conducting groups involve group size, member selection criteria, leadership style, session length, session frequency, and whether the group will be time limited or open ended. Pregroup preparation is essential to familiarize newcomers with expectations, ground rules, and the basics about how the group functions. Other considerations include the degree of heterogeneity versus homogeneity of group membership in terms of demographics, substances of choice, level of functioning, length of sobriety, gender, sexual orientation, and the like. It can be beneficial to mix patients with different substances of choice (e.g., alcohol, stimulants, and opioids) in the same group because it helps to reinforce recognition that it is the addictive disorder, not the drug itself, that brings them together and is the primary focus of the group's work. It is distinctly inadvisable, however, to mix patients with incompatible goals (e.g., abstinence versus harm reduction or moderation) in the same group because it is likely to pose insurmountable challenges to the clinical integrity of the group and jeopardize the recovery of members for whom discussions about controlled substance use may evoke cravings and urges that increase the likelihood of relapse.

Conclusion

Group therapy is a clinically effective and cost-effective psychosocial treatment intervention for substance use dis-

orders. Different group therapy models and approaches provide a range of treatment options, thus allowing treatment to accommodate patients with differing clinical needs.

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Useful Web Sites

Addiction Technology Transfer Center Network: www.attcnetwork.org

National Clearinghouse on Alcohol and Drug Information: www.health.gov

National Institute on Alcohol Abuse and Alcoholism: www.niaaa.nih.gov/publications

SAMHSA's National Registry of Evidence-Based Programs and Practices: www.nrepp.samhsa.gov

Substance Abuse Treatment: Group Therapy (CSAT TIP No. 41): www.ncbi.nlm.nih.gov/books/NBK64220

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CHAPTER 59

Family Therapy in Substance Abuse Treatment

Peter Steinglass, M.D.

During the past three decades a growing clinical and research literature on family issues related to substance abuse has pointed to the important role of family factors in the onset and clinical course of these conditions (O'Farrell and Fals-Stewart 2003; Rowe and Liddle 2003; Velleman et al. 2005). Considerable interest has been generated not only in investigating family aspects of substance abuse but also in applying family therapy techniques to its treatment. Four decades ago alcoholism clinicians by and large ignored families. The current picture is dramatically different. One is now hard-pressed to find a substance abuse treatment program that does not at least give lip service to the importance of including family members in the treatment plan.

Given that substance use disorders create a myriad of emotional responses in families, including grief, despair, angst, helplessness, hopelessness, and uncertainty about the future, all family members clearly have a stake in a successful treatment outcome. One need only mention the incidence rates of physical violence, sexual abuse, financial crises, divorce, effects on children, and the like to make this point (Copello et al. 2005). Hence, it is encouraging that support for the value of including families as components of substance abuse treatment programs is now coming from multiple directions.

The increasing use of family-oriented treatment approaches to substance abuse has also been supported by growing evidence of the efficacy of these approaches (Baucom et al. 1998; Copello et al. 2006; Stanton and Heath 2005). Three conclusions can be drawn from these data:

- The involvement of a nonalcoholic spouse in a treatment program significantly improves participation rates of alcoholic family members in treatment (Stanton 2004).

- Involvement of nonalcoholic spouses also has a positive effect on the likelihood that individuals will alter their drinking behavior after treatment (Rowe and Liddle 2003).
- Psychosocial functioning of *all* family members improves when family treatment approaches are included as a significant component of the treatment plan (O'Farrell and Fals-Stewart 2006).

Overview of Treatment Models

Although a wide array of family-focused treatment approaches for substance use disorders have been suggested, virtually all of them rely on three conceptual models: family systems therapy, family behavioral therapy, and social network therapy. *Family systems therapy* models pay particular attention to ways in which families come to organize their behavior around attempts to adapt to and control the challenges associated with chronic substance abuse. Examples of treatment approaches that have relied heavily on family systems concepts include those of Treadway (1989) and Steinglass et al. (1987) and the systemic-motivational therapy model recently proposed by Steinglass (2009), an approach that integrates family systems ideas with those of motivational interviewing and harm reduction.

Family behavioral treatment models, on the other hand, extend classical conditioning principles to interpersonal behavior. Concepts of reciprocity, coercion, and reinforcement are applied to an analysis of the contingencies that help explain patterns of interaction behavior. Behavioral approaches include the cognitive-behavioral model outlined by McCrady and colleagues (Epstein and McCrady 1998) and the behavioral marital therapy model described by O'Farrell and Fals-Stewart (2006), both of which have been subjected to extensive randomized clinical trials with positive outcome results (Fals-Stewart et al. 2005).

Last, approaches based on social network concepts (*social network therapy* models) emphasize the power not only of family networks but larger social support systems as well in motivating patients to seek treatment and in sustaining change once treatment has been initiated. These approaches are perhaps best represented by the family functioning model proposed by Kaufman and Kaufmann (1989) and the network therapy approach advocated by Galanter (1999).

At the same time, it should also be emphasized that it is unusual to find any of these treatment approaches practiced in their pure forms in clinical settings. Thus, although all of the approaches have been manualized as necessary components of formal treatment outcome research projects, the most salient component of each approach is an emphasis on actively involving spouses and/or other family members as being critical to the successful implementation of treatment at each phase of the treatment process: engagement, assessment, detoxification, post-detoxification stabilization, and rehabilitation. Because the most striking contrasts between family and individual approaches to treatment can be seen during the engagement, assessment, and detoxification phases of treatment, these phases deserve further explication.

Engagement

The clearest example of the power of family approaches to treatment has been the indisputable evidence that working with family members early on significantly increases the likelihood that the substance user will ultimately become engaged in active treatment. A wide num-

ber of such protocols have been proposed, but the most thoroughly researched are the CRAFT (Community Reinforcement And Family Training) and ARISE (A Relational Intervention Sequence for Engagement) programs.

CRAFT works with spouses or concerned significant others in the family to teach methods of positive reinforcement of non-substance-abusing behavior and a restructuring of everyday life to emphasize abstinence as a central component of family behavior (Meyers et al. 1998; Smith and Meyers 2004). In that CRAFT teaches how to avoid confrontation around substance abuse and instead to focus on examples of positive interactions when substances are not present, it relies on techniques similar to those utilized by other successful treatment engagement programs such as motivational interviewing (Miller and Rollnick 2013) or the community reinforcement approach put forward by Sisson and Azrin (1989). A randomized trial of the CRAFT approach compared with Al-Anon facilitation and Johnson Institute family interventions clearly demonstrated its superiority in effectively engaging substance abusers in treatment (64% for CRAFT, 13% for Al-Anon, and 30% for Johnson interventions) (Miller et al. 1999).

ARISE is a stepwise approach in which family members and important members of one's social network are mobilized specifically to influence the engagement of the substance abuser in treatment (Landau et al. 2000). Central to its effectiveness is its emphasis on support for *both* the user and the family member while at the same time minimizing the use of confrontational techniques to address denial (Landau et al. 2004). In this regard it has major overlaps with techniques recommended by Galanter (1999) as key components of his network therapy approach.

It cannot be emphasized too strongly how successful these programs have been in engaging patients in subsequent treatment. For example, the Stanton (2004) review of 11 separate family-oriented programs designed to increase engagement of a substance-abusing family member reported a powerful impact (upward of 65% engagement rates) when compared with wait-list control groups (averaging 6% engagement rates). Liddle (2004) has documented similarly impressive evidence of the effectiveness of engagement of adolescent substance abusers when families are actively involved in the process.

Assessment

Although family therapy assessment strategies may vary somewhat from model to model, because assessment invariably is carried out with *both* patient and family members present, family therapists contend that this significantly improves the quality and accuracy of reported data. For example, basic questions about quantity and frequency of substance use, triggers, descriptions of how behavior changes with substance use, and evidence of withdrawal symptoms or blackouts all can be better understood when these questions are being asked of all family members rather than just the patient alone.

Further, assessment strategies also emphasize aspects of behavior particularly salient to the interface between substance use and family life. As one example, in the treatment approaches advocated by Steinglass and colleagues, explicit questions are asked about the impact of substance use on the family's daily life (routines) and important family rituals (holiday celebrations, vacations, etc.) as well as its role in family problem-solving strategies (Steinglass 2008; Steinglass et

al. 1987). In each of these areas, the goal is to better understand how family behavior has become altered or organized around the on/off cycling of sober/intoxicated interactional behavior, how substance use is talked about within the family (if at all), and how beliefs of family members about the benefits as well as the costs of substance use contribute to substance abuse chronicity.

Detoxification

One of the more unique aspects of family-based substance abuse treatment models is the way the detoxification phase of treatment is approached. Independent of whether one's treatment goal is abstinence or harm reduction, most family-based models once again assume that these goals can be best achieved if they are negotiated with other family members present.

The most common approach is to have the family design a contract to facilitate eliminating or reducing substance use. In some cases the contract is a limited one, for example, a behaviorally oriented spousal contract for disulfiram (Antabuse) use adherence (O'Farrell et al. 1995). But in other cases the goal is a more ambitious family systems–based contract conceptualized as not only detoxifying the substance abuser but also "detoxifying" the psychosocial environment of the entire family (Rohrbaugh et al. 1995; Steinglass et al. 1987). A newer version of "family level detoxification" proposed by Steinglass (2009) has incorporated core concepts from motivational interviewing alongside his earlier (Steinglass et al. 1987) family systems approach.

Similar to the rationale for why assessment is significantly improved when it is carried out with the whole family present, once again the core concept is that independent of whether or not substance abuse started because of the behavior of one individual within the family, by the time it has reached a chronic phase it has become a *central organizer* of so many aspects of family life that enlisting the entire family in the detoxification (or harm reduction) process is an obvious route to follow.

Conclusion

As research data and clinical experience about family therapy approaches to substance use disorders continue to grow, a compelling case can now be made for the incorporation of family-based interventions as core components of treatment of substance use disorders. However, these approaches continue to be underutilized. Hopefully, this is a situation that will be corrected in the future. If this is to occur, however, family therapy skills will have to be included more prominently in the training of addiction clinicians.

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CHAPTER 60

Network Therapy for Substance Use Disorders

Marc Galanter, M.D.

The network therapy approach can be useful in addressing a broad range of patients with addictions characterized by the following clinical hallmarks of substance use disorder: First, when they initiate consumption of their addictive agent, be it alcohol, cocaine, opioids, or depressant drugs, they frequently cannot limit that consumption to a reasonable and predictable level; this phenomenon has been termed "loss of control" by clinicians who treat persons dependent on alcohol or drugs. Second, they consistently demonstrate relapse to the agent of abuse; that is, they attempt to stop using the drug for varying periods of time but return to it despite a specific intent to avoid it.

This treatment approach is not necessary for those abusers who can, in fact, learn to set limits on their use of alcohol or drugs; their use may be treated as a behavioral symptom in a more traditional psychotherapeutic fashion. Nor is it directed at those patients for whom the addictive pattern is most unmanageable (e.g., addicted people with unusual destabilizing circumstances such as homelessness, severe character pathology, or psychosis). These patients may need special supportive care (e.g., inpatient detoxification or long-term residential treatment).

Key Elements of Network Therapy

Three elements are essential to the network therapy technique. The first is a cognitive-behavioral approach to relapse prevention, independently reported to be valuable in addiction treatment (Marlatt and Gordon 1985). In this approach, emphasis is placed on triggers to relapse and behavioral techniques for avoiding them rather than on exploring underlying psychodynamic issues.

Second, support of the patient's natural social network is engaged in treatment. Peer support in Alcoholics Anonymous has long been shown to be an effective vehicle for promoting abstinence,

and the idea of the therapist's intervening with family and friends in starting treatment was employed in one of the early ambulatory techniques specific to addiction. The involvement of spouses has since been shown to be effective in enhancing the outcome of professional therapy.

Third, the orchestration of resources to provide community reinforcement suggests a more robust treatment intervention by providing a support for drug-free rehabilitation. In this relation, Khantzian points to the "primary care therapist" as one who functions in direct coordinating and monitoring roles in order to combine psychotherapeutic and self-help elements. It is this overall management role over circumstances outside as well as inside the office session that is presented to trainees to maximize the effectiveness of the intervention.

Starting a Network

Patients should be asked to bring their spouse or a close friend to the first session. Patients with alcohol use disorder often dislike certain things they hear when they first come for treatment and may deny or rationalize even if they sought help voluntarily. Because of the patient's denial, a significant other is essential to both history taking and implementing a viable treatment plan. A close relative or spouse can often cut through the denial in a way that an unfamiliar therapist cannot and can therefore be invaluable in setting a standard of realism in dealing with the addiction.

Once the patient comes for an appointment, establishing a network is a task undertaken with active collaboration of patient and therapist. The two, aided by those parties who join the network initially, must search for the right balance of members. The therapist must carefully promote the choice of appropriate network members, however, just as the platoon leader selects those who will go into combat.

Defining the Network's Task

As conceived here, the therapist's relationship to the network is like that of a task-oriented team leader rather than that of a family therapist oriented toward insight. The network is established to implement a straightforward task: aiding the therapist in sustaining the patient's abstinence. It must be directed with the same clarity of purpose that a task force is directed with in any effective organization. Competing and alternative goals must be suppressed or at least prevented from interfering with the primary task.

Unlike family members involved in traditional family therapy, network members are not led to expect symptom relief for themselves or self-realization. This lack of expectation prevents the development of competing goals for the network's meetings. It also provides the members protection from having their own motives scrutinized and thereby supports their continuing involvement without the threat of an assault on their psychological defenses.

Adapting Individual Therapy to Network Treatment

Of first importance is the need to address exposure to substances of abuse or to cues that might precipitate alcohol or drug use (Galanter 1993). Both patient and therapist should be sensitive to this

matter and should explore these situations as they arise. Second, a stable social context in an appropriate social environment—one conducive to abstinence with minimal disruption of life circumstances—should be supported. Considerations of minor disruptions in place of residence, friends, or job need not be a primary issue for the patient with character disorder or neurosis, but they cannot go untended in patients with substance use disorders. For a considerable period, the substance abuser is highly vulnerable to exacerbations of the addictive illness and in some respects must be viewed with the considerable caution with which one treats the patient whose psychotic disorder has recently compensated.

Research on Training of Therapists Naive to Addiction Treatment

A course of training for psychiatric residents naive to addiction and ambulatory treatments was undertaken over a period of 2 academic years. Before beginning treatment, the residents were given a structured treatment manual for network therapy and participated in a 13-session seminar on application of the network therapy technique. Patients abusing cocaine were eligible for treatment in this study if they could come for evaluation with a friend or family member who could participate in their treatment. In all, 22 patients were enrolled. The treating psychiatric residents were able to establish requisite networks (i.e., a network with at least one member) for 20 of these patients. The networks had an average of 2.3 members, and the most typical configuration included family members and friends. Supervisors' evaluation of videotapes of the network sessions employing standardized instruments indicated good adherence to the manualized treatment, with effective use of network therapy techniques. The outcome of treatment (Galanter et al. 1997, 2002; Keller et al. 1997) reflected retention and abstinence rates as good as, or better than, those of comparable ambulatory care carried out by therapists experienced in the treatment of alcohol use disorder. The study demonstrated the feasibility of teaching the network technique to therapists naive to addiction treatment.

Research on the Network Approach

Copello et al. (2002) have combined elements of network therapy with social aspects of the community reinforcement approach and relapse prevention referred to as social behavior and network therapy (SBNT) in the treatment of persons with alcohol drinking problems. A number of social skills training strategies are incorporated into the treatment, especially those involving social competence in relation to the development of positive social support for change in alcohol use. Every individual involved in treatment is considered a client in his or her own right, and the person with alcohol problems is referred to as the focal client. The core element of the approach is mobilizing the support of the network even though this may involve network sessions that are conducted in the absence of the focal client.

This approach was extended to a large sample of alcoholic individuals in the United Kingdom Alcohol Treatment Trial (UKATT) project in Great Britain. The UKATT team evaluated the cost-effectiveness of network therapy relative to motivational enhancement ther-

apy (MET). SBNT resulted in a fivefold cost savings in health, social, and criminal justice service expenditures and was similar to cost-effectiveness estimates obtained for MET. The UKATT Research Team (2008) tested a priori hypotheses concerning client-treatment matching effects similar to those tested in Project MATCH (Matching Alcoholism Treatments to Client Heterogeneity). The findings were consistent with Project MATCH in that no hypothesized matching effects were significant. Orford et al. (2009) interviewed a subset of clients (n=397) who participated in this trial to assess their views concerning whether any positive changes in drinking behavior had occurred and to what they attributed those changes. At 3 months after randomization to treatment, patients in network therapy made more social attributions (e.g., involvement of others in supporting behavior change), and MET patients made more motivational attributions (e.g., awareness of the consequences of drinking).

Galanter et al. (2004) evaluated the impact of network therapy relative to a control condition (medical management, MM) among 66 patients who were inducted onto buprenorphine for 16 weeks and then tapered to zero dosage. Network therapy resulted in a greater percentage of opioid-free urines than did MM (65% versus 45%). By the end of treatment, patients in network therapy were more likely to experience a positive outcome relative to secondary heroin use (50% versus 23%). The use of network therapy in office practice may enhance the effectiveness of eliminating secondary heroin use during buprenorphine maintenance.

Conclusion

For moderate or severe substance use disorder, clinicians can enhance the outcome of treatment for certain patients by engaging the support of a network of close relatives and/or friends. This can be done at intervals in conjoint sessions with the patient.

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CHAPTER 61

Pain and Addiction

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In this chapter I focus on several dimensions of the intersection between chronic pain and addiction. The co-occurrence of pain and opioid addiction is a clinically challenging area that has received increasingly close consideration in the past several years. Prescription opioid addiction currently represents a major public health concern in light of the widespread abuse and misuse of opioids for their psychotropic effects both in the United States and in many countries throughout the world. The interface between the legitimate medical use of opioids and the phenomena associated with abuse and addiction is clinically challenging, leading to uncertainty about the appropriate role of these drugs in the treatment of pain.

In this review, I consider screening tools and monitoring techniques that can be implemented to minimize risks of opioid misuse among chronic pain patients. I also consider common comorbidities in pain patients, along with the role for buprenorphine-naloxone in treating concurrent chronic pain and prescription opioid abuse.

Epidemiology of Chronic Pain in the United States

Chronic pain is typically defined clinically as pain that persists or recurs for more than 3 months (Verhaak et al. 1998). It is a significant and increasing public health issue. The most common type of chronic pain syndrome is low back pain, affecting 25%–50% of primary care populations (Reid et al. 2002). Other prevalent types of chronic pain include musculoskeletal, osteoarthritis, and injury-related pain. Somewhat less common are headache, diabetic neuropathy, and spinal stenosis. Chronic pain affects more than 100 million Americans. There is thus an enormous population at potential risk for prescription opioid misuse.

Pain-related lost productivity in the workplace and work absence cost employers more than $61 billion annually, and pain is the most frequent cause of disability for Americans (Stewart et al. 2003). A recent large meta-analysis of

pan-Europe epidemiological data found that the 1-month prevalence of moderate-to-severe noncancer pain was 19% (Reid et al. 2011). In addition to decreased occupational functioning, individuals with chronic pain may suffer iatrogenic consequences of treatments (e.g., failed back surgery or gastrointestinal bleeds from overuse of nonsteroidal anti-inflammatory drugs) as well as depression, anxiety, insomnia (McCarberg and Billington 2006), and comorbid alcohol or substance use. Overall, individuals with chronic pain experience decreased quality of life and functional losses across several domains.

U.S. Trends in Opioid Prescribing and Epidemiology of Prescription Opioid Abuse

In response to advocacy by physicians and professional societies addressing the perceived undertreatment of chronic pain, two historical events led to dramatic increases in opioid prescribing in the United States: in the late 1990s, state medical boards liberalized laws governing opioid prescribing for the treatment of chronic noncancer pain, and the Joint Commission on Accreditation of Healthcare Organizations in 2000 introduced new pain management standards permitting the use of opioid analgesics for chronic noncancer pain (Manchikanti et al. 2010). Other factors contributing to increased opioid prescribing were the development in the 1990s of high-potency opioid pills and the current nature of financial reimbursement for medical care, which is tied to the number of clinical encounters and does not reward engaging in time-consuming, nonreimbursable assessments of risks versus benefits (Gallagher and Rosenthal 2008).

Total retail sales of commonly used opioid medications (including codeine, morphine, hydromorphone, hydrocodone, methadone, oxycodone, and fentanyl base) increased 149% from 1997 to 2007, with increases of 866% for oxycodone and 1,293% for methadone (Manchikanti et al. 2010). The National Survey on Drug Use and Health reports that among individuals ages 12 and older, 4.6% have used prescription opioids nonmedically in the past year (U.S. Department of Health and Human Services 2011). The most common source for those misusing opioids to obtain pain relievers is from a friend or relative for free (60%), followed by obtaining prescriptions from one physician (17%). Thus, opioid prescribers represent an important source for abused opioids. Of further concern is the finding that 17.1% of substance abusers cite pain medication as being the first substance they abused, suggesting that prescription opioids are a gateway drug (U.S. Department of Health and Human Services 2010). In sum, efforts to more aggressively manage pain have resulted in substantial rises in the prescribing and misuse of high-potency opioids such as hydrocodone and oxycodone.

Barriers to Providing Effective Pain Management

Despite the prevalence of chronic pain, many health care providers wish to avoid becoming involved in its treatment for several reasons. Individuals with chronic pain who have seen many physicians without relief may be perceived as less than honest concerning their symptoms.

Also, chronic pain does not produce sympathetic arousal; the absence of objective signs may cast doubt on reported symptoms. Pain management is complicated and requires a multidisciplinary approach, which often receives poor reimbursement. Finally, physicians feel vulnerable in the face of increased regulatory scrutiny and an epidemic of prescription drug abuse.

Challenges for opioid prescribing in the primary care setting include balancing the risks of undertreating pain against those of contributing to opioid abuse and dependence. Undertreatment of pain may arise from several factors, including inadequate training in pain management (Saroyan et al. 2011; Tousignant-Laflamme et al. 2012), drug interactions affecting metabolism of opioids (Gallagher and Rosenthal 2008), and concerns regarding abuse liability (Webster and Fine 2010). Risks of prescribing include overcoming such factors as opioid tolerance, use of opioids for their psychoactive properties, and opioid-induced hyperalgesia (Stanos et al. 2012).

In response to the disturbing increases in prescription opioid abuse since the late 1990s, the U.S. Food and Drug Administration (FDA) has proposed the implementation of mandatory risk evaluation and mitigation strategies (REMS). REMS would require opioid prescribers to obtain pain-related continuing medical education, provide mandatory patient education, document and monitor ongoing therapies, and maintain patient registries. A recent survey designed to assess the impact of REMS on prescribing found that a substantial percentage of family practice physicians (N=2,800) planned to discontinue prescribing opioids if required to comply with certain REMS components (Slevin and Ashburn 2011), such as documentation of efficacy, safety, and aberrant drug-related behaviors (10.4%) or the requirement to maintain and periodically update an opioid patient registry every 6 months (18.3%). These findings suggest that REMS could have the unintended consequence of decreasing legitimate medical access to these medications.

Risks Related to Opioid Prescribing

The risks of withholding effective pain management include all of the physical and emotional consequences of persistent pain. These include reduced quality of life from unmanageable pain, depression, and anxiety as well as significant functional limitations. In the elderly and patients with cardiac risk factors, sympathetic overdrive resulting from undertreated pain can also pose risks for tachycardia and cardiac arrhythmias. Undertreatment of pain in the primary care setting arises from lack of training in pain management, lack of collaboration with pain specialists, and concerns about regulatory consequences (Stanos et al. 2012; Webster and Fine 2010).

However, there are also many risks attending opioid prescribing, including sexual dysfunction and hypogonadism, increased tolerance, and hyperalgesia, as well as opioid abuse and diversion. The prescribing clinician is faced with the need to balance providing opioid analgesics for legitimate medical needs against the ambiguities and risks of opioid abuse. Since there is no definitive screening test to predict risk of problematic opioid use, the current recommendation is to take a "universal precautions" approach (Gourlay et al. 2005), which will be detailed in the next section. This clinical approach involves careful baseline assessments that permit

triaging patients into categories of risk, then setting reasonable limits for the terms of opioid prescribing.

The greatest risk associated with increased opioid prescribing is that of opioid overdose and death. Morbidity and mortality, including emergency department (ED) visits, have risen substantially and linearly with the availability of opioids. By 2008, deaths due to opioid analgesics in the United States reached 15,000, exceeding those from cocaine or heroin (U.S. Department of Health and Human Services, 2005) and surpassing motor vehicle accidents as the most frequent cause of death in some states (Paulozzi and Xi 2008).

The U.S. Centers for Disease Control and Prevention have reported that methadone was involved in more than 30% of overdose deaths linked to the use of prescription opioids in 2009, although methadone represented only 2% of painkiller prescriptions. Although methadone—a synthetic opioid agonist at the μ and δ receptors—has been used for more than 40 years as a primary pharmacological treatment for heroin addiction in the United States, it is only in the past decade that it has been widely used as an analgesic. Because of its low cost, methadone has been a preferred option for many insurance companies and state Medicaid formularies. However, methadone carries many specific risks that make it the least safe option among opioid analgesics. Its long and unpredictable half-life (up to 36 hours) greatly exceeds the analgesic duration of action (6–9 hours) and leads to the risk of accumulation and respiratory depression, especially during induction. In addition, methadone may interact with benzodiazepines, often prescribed to patients with pain, to heighten the risk for unintentional overdose (Webster 2010). Methadone also has the potential to induce cardiac arrhythmias, including prolonged QT and torsade de pointes, thus requiring electrocardiogram monitoring. Methadone should not be the first choice in the treatment of chronic pain and should not be prescribed to opioid-naive individuals.

Screening for Risk of Opioid Abuse in Pain Patients

Universal precautions is a uniform approach intended to reduce stigma, improve patient care, and minimize risks by asking patients about personal and family history of substance abuse (often using screening tools), obtaining informed consent for treatment (usually with a formal written treatment agreement), performing ongoing reassessment of benefits from a trial of opioid therapy, and providing complete documentation of the evaluation and reassessments (Yanni et al. 2008).

By using universal precautions, clinicians can triage individuals to different categories (low, medium, and high risk) in terms of addiction liability. Low-risk patients with chronic noncancer pain have no history of substance abuse and lack any major psychiatric comorbidity. Such individuals do not exhibit aberrant behaviors and can be managed in a primary care setting. Medium-risk patients may have a prior history of substance abuse, family history of substance abuse, or psychiatric comorbidity. These individuals can be managed in a primary care setting, particularly with consultation from an addiction specialist or psychiatrist. High-risk patients with active addictive disorders are at an increased risk for aberrant behaviors and should be referred to an addiction specialist. It is recommended that clinicians prepare

treatment agreements that delineate rules such as having no early refills and requirements for urine toxicology. Written medication agreements should make explicit the patient's responsibilities in medication adherence, use of only a single opioid prescriber, consent for random urine toxicology testing, and the consequences of failing to adhere to these policies (i.e., supervised taper from opioids and/or referral to another provider or program).

The use of empirically validated opioid risk screening tools can be extremely helpful in identifying potential risk factors in patients considered for opioid therapy. The most widely used screening instruments are 1) the Prescription Drug Use Questionnaire (PDUQ), 2) the Screener and Opioid Assessment for Patients with Chronic Pain (SOAPP), 3) the Pain Assessment and Documentation Tool (PADT), and 4) the Opioid Risk Tool (ORT). The PDUQ (Compton et al. 1998, 2008) assesses for the presence of risk-related behaviors such as hoarding pills, using analgesics to relieve nonpain symptoms, and combining opioid analgesics with alcohol or drugs. The SOAPP (Butler et al. 2004) captures a history of substance use, legal problems, craving, heavy smoking, and mood swings. The PADT (Passik et al. 2004) assesses four domains: 1) pain relief, 2) patient functioning, 3) adverse events, and 4) drug-related behaviors. Finally, the ORT uses risk factors (personal and family history of substance abuse, age, preadolescent sexual abuse, and Axis I disorders) to stratify patients into low, moderate, and high risk of displaying aberrant behaviors (Webster and Webster 2005).

Chronic pain syndromes carry a high degree of psychiatric comorbidity, including depression (37%), anxiety (25%), substance use disorders (12%; Knaster et al. 2012), somatization, and borderline personality disorder (McWilliams and Higgins 2013). Patients with significant psychiatric comorbidity and substance use are more likely to stay on opioids and to receive higher dosages (Krashin et al. 2013). Many patients in primary care or pain management centers would benefit from initial screening for mood, anxiety, and concurrent addiction disorders.

Identifying Aberrant Behaviors Among Patients With Chronic Pain

Given that many patients taking opioids may not exhibit symptoms of psychological dependence such as craving or other overt addictive behaviors (Fishbain et al. 1992), special attention is needed to assess potential opioid abuse in pain patients. Portenoy and Payne (1997) have developed a list of aberrant drug-related behaviors that suggest an addiction disorder in pain patients. These include 1) selling prescription drugs, 2) forging prescriptions, 3) stealing drugs, 4) injecting oral formulations, 5) obtaining prescription drugs from nonmedical sources, 6) concurrent abuse of alcohol or illicit drugs, 7) dose escalations or failing to comply with the prescribed regimen despite warnings, 8) "losing" prescribed medication, 9) seeking prescriptions from other clinicians or EDs, 10) deterioration in ability to function that appears related to drug use, and 11) resisting changes in opioid therapy despite adverse effects from the drug.

Certain patient characteristics observed clinically also raise concerns of an addictive process and should prompt adher-

ence monitoring. Among these behaviors are demanding behavior with respect to medication; unusual appearance, behavior, or knowledge of medications; giving evasive answers on history; and refusing further diagnostic workup.

Buprenorphine-Naloxone for Treatment of Opioid Dependence and Chronic Pain

Patients with concurrent chronic pain and opioid addiction present a therapeutic challenge. For such patients, it is essential to identify a pain management strategy that will reduce the risk of relapse while providing adequate analgesia for the long term. Buprenorphine is a distinct long-acting partial μ opioid agonist FDA approved in 2002 as a maintenance agonist for the treatment of opioid addiction (Schedule III). Buprenorphine is the first agent available in the United States for office-based treatment of opioid dependence under the Drug Addiction Treatment Act of 2000.

Buprenorphine is well absorbed sublingually and dissociates slowly from opioid receptors, resulting in a long duration of action (Sporer 2004). At higher doses, its agonist effects plateau, thus limiting the maximal analgesic effect and respiratory depression (Sporer 2004). Analgesic doses of buprenorphine are usually given in divided daily doses totaling 8–32 mg because the analgesic duration is 6–9 hours (Alford et al. 2006). Several studies have shown that buprenorphine reduces illicit opioid use and craving, has few side effects, and is acceptable to most patients. The combination formulation Suboxone (buprenorphine-naloxone) is a sublingual film recommended for use in opioid abusers. Inclusion of naloxone in this preparation discourages street diversion for parenteral administration. The pharmacological effects of the monoformulation and combination formulation, when these formulations are taken as directed, do not differ (Chiang and Hawks 2003; Harris et al. 2004).

For patients with chronic pain and concurrent opioid abuse, there are several advantages to use of buprenorphine as a maintenance medication, including that it 1) is associated with less analgesic tolerance than other opioids and can be combined with other μ agonists (Davis 2012), 2) has a safer cardiac profile than methadone and does not prolong the QT interval, 3) has a ceiling effect on respiratory depression, 4) results in less cognitive impairment and constipation than short-acting opioids, 5) has milder withdrawal symptoms, and 6) does not adversely affect the immune system.

Buprenorphine can be effective as monotherapy in cases of concurrent opioid addiction and moderate or moderately severe chronic pain (Daitch et al. 2012; Neumann et al. 2013). Among patients with chronic pain and opioid use disorder treated with buprenorphine-naloxone, successful retention at 12 weeks was predicted by being of older age, having lifetime major depressive disorder, having used opioids only orally or sublingually, and having received no prior treatment for opioid dependence (Dreifuss et al. 2013). Buprenorphine maintenance has also been found to lead to reductions in the reinforcing effects of shorter-acting opioids (Jones et al. 2011), suggesting that buprenorphine reduces the abuse liability of short-acting opioids, whether they are taken nonmedically or for the purpose of treating an acute exacerbation of pain.

Conclusion

Prescription opioids are among the most effective medications for the management of moderate to severe pain. However, their current widespread use for long-term noncancer pain has been associated with a marked increase in the abuse of prescription opioids since the late 1990s, with sharp recent rises in morbidity and mortality. Screening instruments have been developed to define objective risk factors for opioid abuse, but definitive predictors are lacking. Risk of iatrogenic addiction with long-term opioid analgesics is also not well characterized. The majority of pain patients treated with opioids are physically dependent and will experience characteristic withdrawal symptoms on abrupt drug cessation but are not addicted.

Some pain patients maintained on opioids will develop opioid use disorder (American Psychiatric Association 2013), which may be characterized by impaired control over opioid use, continued use despite harm, and craving. Aberrant medication-taking behaviors may signal addiction. On the other hand, such behaviors may reflect inadequate analgesia (pseudoaddiction) or misuse of opioid analgesics to treat depression, anxiety, or personality disorders (Gourlay et al. 2005).

For patients who do develop opioid addiction, opioid substitution with buprenorphine-naloxone and management of addiction risk through the use of medication agreements and adherence monitoring can be safely and effectively carried out in an office setting. There is a clear imperative to develop analgesics with lower abuse liability, and current research efforts are also targeting the development of better methods to detect patients at risk for developing addiction.

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CHAPTER 62

Gambling Disorder

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Gambling disorder is characterized by a persistent and recurrent maladaptive pattern of gambling behavior, preoccupation with gambling activities, loss of control, and continued gambling despite problems in social or occupational functioning (Box 62–1). It is associated with significant financial losses, legal problems, and disrupted interpersonal and familial relationships. Individuals with gambling disorder are also at increased risk for suicide attempts (Phillips et al. 1997), new-onset comorbid psychiatric disorders (Kessler et al. 2008), and several medical conditions (Morasco et al. 2006).

Box 62–1. DSM-5 Diagnostic Criteria for Gambling Disorder

312.31 (F63.0)

A. Persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period:

1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
2. Is restless or irritable when attempting to cut down or stop gambling.
3. Has made repeated unsuccessful efforts to control, cut back, or stop gambling.
4. Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble).
5. Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed).
6. After losing money gambling, often returns another day to get even ("chasing" one's losses).

7. Lies to conceal the extent of involvement with gambling.
8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling.
9. Relies on others to provide money to relieve desperate financial situations caused by gambling.

B. The gambling behavior is not better explained by a manic episode.

Specify if:

Episodic: Meeting diagnostic criteria at more than one time point, with symptoms subsiding between periods of gambling disorder for at least several months.

Persistent: Experiencing continuous symptoms, to meet diagnostic criteria for multiple years.

Specify if:

In early remission: After full criteria for gambling disorder were previously met, none of the criteria for gambling disorder have been met for at least 3 months but for less than 12 months.

In sustained remission: After full criteria for gambling disorder were previously met, none of the criteria for gambling disorder have been met during a period of 12 months or longer.

Specify current severity:

Mild: 4–5 criteria met.

Moderate: 6–7 criteria met.

Severe: 8–9 criteria met.

Despite its serious consequences (e.g., Kessler et al. 2008; Petry et al. 2005), gambling disorder is rarely diagnosed and even more rarely treated (Slutske 2006). Less than 10% of individuals with gambling disorder ever seek treatment (Slutske 2006), probably because of a combination of ambivalence about seeking treatment on the part of the patients and limited access for those who wish to seek it. Although some data suggest that many individuals with gambling disorder recover without formal treatment (Hodgins and el-Guebaly 2000; Slutske et al. 2003), there is no available information on the time to remission in natural recovery or the risk of recurrence. Fortunately, despite our limited knowledge about the epidemiology and etiology of gambling disorders, a growing body of literature has examined pharmacological and psychological treatments for gambling disorder.

Cognitive-Behavioral Approaches

At present, cognitive-behavioral therapy (CBT) is the treatment with the strongest evidence of efficacy for gambling disorder. CBT approaches have been shown to help reduce gambling severity, financial loss, and gambling frequency and to increase the likelihood of remission (Cowlishaw et al. 2012). A recent meta-analysis identified 11 randomized trials comparing CBT with controls and found that the effects of the interventions were medium to very large at 0–3 months posttreatment (Cowlishaw et al. 2012).

CBT approaches are based on the premise that gambling disorder is caused by a combination of maladaptive learned models of reinforcement and distorted cognitions held by the patients. Two of

the most important examples of cognitive distortions (also called "cognitive errors" or "thinking errors") are attributional biases and the "gambler's fallacy." In the case of *attributional biases,* individuals overestimate dispositional factors such as their skills and underestimate situational factors such as luck when attempting to explain their wins. The *gambler's fallacy* refers to the belief that a win is due after a series of losses and therefore, the only way for the individual to recover his or her losses is to continue gambling. Other examples of cognitive distortions include inaccurate beliefs about statistical independence and randomness, superstitious beliefs, selective memory (selectively recalling wins but having difficulty recalling losses), the illusion of control over luck, and using illusory associations in the attempt to predict outcomes (Ladouceur et al. 2001, 2003). The effect of these cognitive distortions on the maintenance of disordered gambling is further amplified by the intermittent positive reinforcement (e.g., financial gain) and negative reinforcement, such as temporary escape from negative emotional states, provided by gambling behavior (Sharpe and Tarrier 1993).

CBT generally comprises five major components: psychoeducation, increasing awareness about cognitive errors, challenging the validity of irrational cognitions, functional analysis, and cognitive restructuring. Many individuals with gambling disorder lack awareness about the random nature of gambling. It is often useful to instruct them or remind them about the independence of events. For example, slot machines work using complex random number generators, so the time since the last win is not a good predictor of the time of the next win.

Psychoeducation about the randomness of gambling will help the patients with the next component of therapy, which is to identify their own cognitive distortions and their own gambling behavior. A Socratic-type interview style is often used to increase awareness about one's own cognitive errors and superstitions: Do you have a specific ritual before pressing the button of a slot machine? Are you convinced that a machine "is due to win" if it has been used a certain number of times without winning?

Once the distorted cognitions have been identified, the next step is to challenge the validity of the gambler's current beliefs as part of cognitive restructuring. For example, how accurate have they been in predicting previous wins? If the patient has a gambling strategy, how is it that this strategy leads him or her to lose money on average? What is the evidence that this strategy helped the gambler outsmart chance and change the odds in his or her favor? Although many patients with gambling disorder appear to readily agree about the flaws in their reasoning, most of those patients do not truly doubt the validity of their beliefs. It generally takes time, several therapy sessions, and some empirical evidence (e.g., having the patient predict the outcome of coin flips or dice rolls) to help patients question their cognitions.

It is often useful to include as part of CBT a functional analysis to complement identification and challenging of cognitive distortions. A functional analysis consists of identifying triggers or precipitants to gambling. These generally include situations (e.g., receiving a paycheck), emotions (e.g., sadness, boredom, elation), or people (e.g., work colleagues who also gamble, phone calls from a broker). Gambling episodes are broken into positive and negative consequences as well as short-term and long-term consequences. The functional analysis serves the triple purpose of helping patients discover their triggers, monitor their be-

havior, and conduct a cost-benefit analysis of that behavior.

The final step in the therapy is to apply in vivo the skills that have been learned and rehearsed during the therapy. This step is the most difficult and consequently the one that generally requires the most time. CBT approaches often include a component of relapse prevention adapted from Marlatt's model for the treatment of substance use disorders (Marlatt and George 1984). The possibility of relapsing is discussed with the patient. High-risk situations and thinking errors associated with these situations are identified, and plans to avoid those situations or seek immediate help are developed as part of the treatment (Ladouceur and Lachance 2007).

An important limitation of published work on CBT is the scarcity of data on long-term outcome. To date, the only study that compared outcomes of individuals treated with CBT with those of a control group at 9–12 months follow-up failed to find significant differences across the groups. Thus, there is a need to obtain further information on the long-term efficacy of CBT and, if necessary, modify existing approaches to increase the durability of its effects.

A second important limitation of existing CBT approaches is that although they are efficacious for patients who remain in treatment, dropout rates have been high in most trials, limiting the effectiveness of these approaches. Future research should identify ways to improve retention and outcome of CBT.

Motivational Interviewing

One of the potential reasons for the high dropout rates in CBT studies may be patients' ambivalence toward quitting gambling. This has led to a growing interest in the use of motivational interviewing (MI) for the treatment of gambling disorder. Motivational interviewing techniques work from the assumption that a primary obstacle to change is ambivalence about changing rather than maintaining a specific behavior. The goal of MI is to reduce this ambivalence and to strengthen commitment to change. MI has been tested as a stand-alone treatment (Carlbring and Smit 2008; Diskin and Hodgins 2009; Hodgins et al. 2009a, 2009b) and integrated with other approaches for gambling disorder, including CBT and personalized feedback (Grant et al. 2011; Oei et al. 2010; Petry et al. 2008; Wulfert et al. 2006). The few studies that applied MI have provided evidence of some beneficial effects from therapy in terms of reduced financial loss from gambling and less frequent gambling. Overall, these results suggest the need for more work in this area to better delineate the populations for which MI may work best and to determine when it can be provided as a stand-alone versus an integrated treatment.

Psychodynamic Approach

Psychoanalytical therapy was one of the early approaches to the treatment of gambling disorder. Some psychoanalytical perspectives on gambling disorder focused on narcissistic fantasies involving grandiosity and entitlement (Simmel 1920), whereas other authors felt that individuals with gambling disorder had an unconscious desire to lose (Bergler 1958) or that gambling disorder constituted a manic defense against helplessness and depression (Boyd and Bolen 1970).

More recently, Rosenthal and Rugle (1994) proposed a psychodynamic model for the treatment of gambling disorder that integrates a traditional psychodynamic approach with an addiction-based model. Their approach emphasizes the importance of abstinence, which is achieved by identifying reasons for gambling, and clarifies gambling defensive and adaptive purposes. Central to this approach is the belief that gambling, and the fantasies associated with it, is a way to avoid, compensate for, or negate intolerable affects. At present, systematic outcome studies of gamblers treated psychodynamically are lacking.

Pharmacological Interventions

Several medication classes have been studied for the treatment of gambling disorder, including opioid antagonists, antidepressants, mood stabilizers, antipsychotics, and glutamatergic compounds. A meta-analysis of 16 trials found that pharmacological treatments were superior to placebo (Pallesen et al. 2007), but the evidence supporting a single agent is limited to date, and no drug has received regulatory approval as a treatment for gambling disorder.

Initial pharmacological studies for gambling disorder focused on antidepressants. Open trials of several SSRIs suggested that they might be efficacious for gambling disorder, but the results of placebo-controlled trials have yielded more mixed results (Blanco et al. 2002; Grant et al. 2003; Hollander et al. 2000; Kim et al. 2002; Sáiz-Ruiz et al. 2005). Similarly, a double-blind placebo-controlled study failed to demonstrate the superiority of bupropion over placebo (Black et al. 2007).

More recently, opioid antagonists (naltrexone and nalmefene) have been investigated on the basis of the premise that opioids may help decrease the reinforcing properties of gambling. Two double-blind placebo-controlled studies supported the efficacy of naltrexone (at dosages of 50–150 mg) for the treatment of gambling disorder (Grant et al. 2008; Kim et al. 2001), whereas the results of the two multicenter placebo-controlled trials of nalmefene (at dosages as low as 25 mg) yielded more mixed results (Grant et al. 2006, 2010). Overall, these results suggest that opioid antagonists may be efficacious for some patients, but they also indicate the need to develop better targeted, more powerful treatments.

Mood stabilizers (sustained-release lithium carbonate, valproate, and topiramate) for the treatment of gambling disorder have also yielded mixed results. Preliminary data from open-label trials have shown promise for glutamatergic compounds such as memantine and *N*-acetylcysteine, although placebo-controlled trials are needed to confirm the efficacy of these agents.

In summary, studies of the pharmacological treatment of gambling disorder suggest that several medications have modest efficacy and may be useful in the treatment of a subgroup of patients. However, they also point to an urgent need to improve our understanding of the neurobiology of gambling disorder to allow for the development of more precise treatments. In addition, similar to findings in psychotherapy trials, medication trials of gambling disorder have been hampered by high dropout rates. Interventions that help increase retention in medication treatment could increase our ability to detect efficacious treatments in research studies and to improve the outcome of gambling disorder in clinical practice.

Gamblers Anonymous

Gamblers Anonymous (GA) is a 12-step program adapted from Alcoholics Anonymous (AA). Similar to AA, GA utilizes peer support to help maintain abstinence from gambling. GA is probably the most common intervention for gambling disorder, with more than 1,000 chapters in the United States alone. However, randomized controlled trials to support the efficacy of GA are missing, and retrospective reports indicate that 70%–90% of GA attendees drop out and that less than 10% become active members. Moreover, only 8% of attendees achieve a year or more of abstinence. Thus, while GA alone may be efficacious for some individuals, combining professional therapy and GA participation may improve retention and abstinence for most individuals (Petry and Armentano 1999).

Conclusion

Although there is still a paucity of evidence for effective treatments, several therapeutic strategies have been tested for gambling disorder. At present, cognitive-behavioral therapy approaches have the strongest empirical support (Oakley-Browne et al. 2000). There is also preliminary evidence for some benefits from motivational interviewing therapy (Cowlishaw et al. 2012). However, most of these studies utilize small and selected samples, making results difficult to generalize. Evidence for pharmacological intervention is also very limited, although there have been some promising results. As our understanding of neurobiology and psychological underpinnings continues to progress, it will be possible to develop more effective, precise, and personalized treatment for gambling disorder.

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PART XI

Neurocognitive Disorders

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The neurocognitive disorders diagnostic class of the *Diagnostic Manual of Mental Disorders,* 5th Edition (DSM-5; American Psychiatric Association 2013) focuses on neurological and medical conditions that impair cognition, produce neuropsychiatric disturbances, and substantively limit an individual's ability to meet the demands of everyday life in a flexible and adaptive manner. Although some of these conditions (i.e., delirium) compromise neuropsychiatric health transiently, they often are associated with significant morbidity and mortality. In these circumstances, prompt diagnosis and effective treatment reduce medical complications and prevent deaths. Many other neurocognitive disorders (i.e., those due to neurodegenerative conditions), once acquired, are permanent and relentlessly progressive. The moment at which these types of neurocognitive disorders are communicated to patients and their loved ones is life altering. Clinicians therefore owe a debt of responsibility to patients and their families to ensure that neurocognitive disorder diagnoses made are accurate and treatments rendered thereafter are evidence-informed.

The reformulation of the cognitive disorders chapter of the *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000) as neurocognitive disorders in DSM-5 presents both an exciting opportunity for advancing psychiatric nosology and a daunting challenge when describing the treatments of these conditions. Concerns about the stigmatizing nature of the term dementia (George et al. 2011) are addressed by reclassifying these conditions as neurocognitive disorders, which includes delirium, those previously described as dementias, and other unspecified disturbances of cognition. The new criteria emphasize the implications of neu-

rocognition on functional status through the use of the qualifiers "mild" (see Box 1) and "major" (see Box 2). They also acknowledge explicitly the probabilistic nature of diagnosis in the absence of neuropathological examination by applying "probable" and "possible" specifiers to many of these disorders.

Box 1. DSM-5 Diagnostic Criteria for Mild Neurocognitive Disorder

A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
   2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Specify whether due to:

Alzheimer's disease (DSM-5, pp. 611–614)
Frontotemporal lobar degeneration (DSM-5, pp. 614–618)
Lewy body disease (DSM-5, pp. 618–621)
Vascular disease (DSM-5, pp. 621–624)
Traumatic brain injury (DSM-5, pp. 624–627)
Substance/medication use (DSM-5, pp. 627–632)
HIV infection (DSM-5, pp. 632–634)
Prion disease (DSM-5, pp. 634–636)
Parkinson's disease (DSM-5, pp. 636–638)
Huntington's disease (DSM-5, pp. 638–641)
Another medical condition (DSM-5, pp. 641–642)
Multiple etiologies (DSM-5, pp. 642–643)
Unspecified (DSM-5, p. 643)

Coding note: For mild neurocognitive disorder due to any of the medical etiologies listed above, code **331.83 (G31.84).** Do *not* use additional codes for the presumed etiological medical conditions. For substance/medication-induced mild neurocognitive disorder, code based on type of substance; see "Substance/Medication-Induced Major or Mild Neurocognitive Disorder." For unspecified mild neurocognitive disorder, code **799.59 (R41.9).**

Specify:

Without behavioral disturbance: If the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.

With behavioral disturbance *(specify disturbance):* If the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g., psychotic symptoms, mood disturbance, agitation, apathy, or other behavioral symptoms).

Box 2. DSM-5 Diagnostic Criteria for Major Neurocognitive Disorder

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
   2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Specify whether due to:

Alzheimer's disease (DSM-5, pp. 611–614)
Frontotemporal lobar degeneration (DSM-5, pp. 614–618)
Lewy body disease (DSM-5, pp. 618–621)
Vascular disease (DSM-5, pp. 621–624)
Traumatic brain injury (DSM-5, pp. 624–627)
Substance/medication use (DSM-5, pp. 627–632)
HIV infection (DSM-5, pp. 632–634)
Prion disease (DSM-5, pp. 634–636)
Parkinson's disease (DSM-5, pp. 636–638)
Huntington's disease (DSM-5, pp. 638–641)
Another medical condition (DSM-5, pp. 641–642)
Multiple etiologies (DSM-5, pp. 642–643)
Unspecified (DSM-5, p. 643)

Coding note: Code based on medical or substance etiology. In some cases, there is need for an additional code for the etiological medical condition, which must immediately precede the diagnostic code for major neurocognitive disorder, as follows:

Etiological subtype	**Associated etiological medical code for major neurocognitive disorder**[a]	**Major neurocognitive disorder code**[b]	**Mild neurocognitive disorder code**[c]
Alzheimer's disease	Probable: 331.0 (G30.9) Possible: no additional medical code	Probable: 294.1x (F02.8x) Possible: 331.9 (G31.9)[c]	331.83 (G31.84) (Do not use additional code for Alzheimer's disease.)
Frontotemporal lobar degeneration	Probable: 331.19 (G31.09) Possible: no additional medical code	Probable: 294.1x (F02.8x) Possible: 331.9 (G31.9)[c]	331.83 (G31.84) (Do not use additional code for frontotemporal disease.)

Etiological subtype	Associated etiological medical code for major neurocognitive disorder[a]	Major neurocognitive disorder code[b]	Mild neurocognitive disorder code[c]
Lewy body disease	Probable: 331.82 (G31.83) Possible: no additional medical code	Probable: 294.1x (F02.8x) Possible: 331.9 (G31.9)[c]	331.83 (G31.84) (Do not use additional code for Lewy body disease.)
Vascular disease	No additional medical code	Probable: 290.40 (F01.5x) Possible: 331.9 (G31.9)[c]	331.83 (G31.84) (Do not use additional code for the vascular disease.)
Traumatic brain injury	907.0 (S06.2X9S)	294.1x (F02.8x)	331.83 (G31.84) (Do not use additional code for the traumatic brain injury.)
Substance/ medication-induced	No additional medical code	Code based on the type of substance causing the major neurocognitive disorder[c, d]	Code based on the type of substance causing the mild neurocognitive disorder[d]
HIV infection	042 (B20)	294.1x (F02.8x)	331.83 (G31.84) (Do not use additional code for HIV infection.)
Prion disease	046.79 (A81.9)	294.1x (F02.8x)	331.83 (G31.84) (Do not use additional code for prion disease.)
Parkinson's disease	Probable: 332.0 (G20) Possible: No additional medical code	Probable: 294.1x (F02.8x) Possible: 331.9 (G31.9)[c]	331.83 (G31.84) (Do not use additional code for Parkinson's disease.)
Huntington's disease	333.4 (G10)	294.1x (F02.8x)	331.83 (G31.84) (Do not use additional code for Huntington's disease.)
Due to another medical condition	Code the other medical condition first (e.g., 340 [G35] multiple sclerosis)	294.1x (F02.8x)	331.83 (G31.84) (Do not use additional codes for the presumed etiological medical conditions.)

Etiological subtype	Associated etiological medical code for major neurocognitive disorder[a]	Major neurocognitive disorder code[b]	Mild neurocognitive disorder code[c]
Due to multiple etiologies	Code all of the etiological medical conditions first (with the exception of vascular disease)	294.1x (F02.8x) (Plus the code for the relevant substance/medication-induced major neurocognitive disorders if substances or medications play a role in the etiology.)	331.83 (G31.84) (Plus the code for the relevant substance/medication-induced mild neurocognitive disorders if substances or medications play a role in the etiology. Do not use additional codes for the presumed etiological medical conditions.)
Unspecified neurocognitive disorder	No additional medical code	799.59 (R41.9)	799.59 (R41.9)

[a]Code first, before code for major neurocognitive disorder.
[b]Code fifth character based on symptom specifier: x0 without behavioral disturbance; x1 with behavioral disturbance (e.g., psychotic symptoms, mood disturbance, agitation, apathy, or other behavioral symptoms).
[c]**Note:** Behavioral disturbance specifier cannot be coded but should still be indicated in writing. [d]See "Substance/Medication-Induced Major or Mild Neurocognitive Disorder."

Specify:

Without behavioral disturbance: If the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.

With behavioral disturbance *(specify disturbance):* If the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g., psychotic symptoms, mood disturbance, agitation, apathy, or other behavioral symptoms).

Specify current severity:

Mild: Difficulties with instrumental activities of daily living (e.g., housework, managing money).

Moderate: Difficulties with basic activities of daily living (e.g., feeding, dressing).

Severe: Fully dependent.

The influence of these modifications to psychiatric nosology will be substantial and usefully advance research and practice in the clinical neurosciences. The introduction of new diagnostic terms also necessarily creates a gap between the clinical work—now anchored to these terms—and the treatment literature published to date. Clinicians attempting to provide evidence-informed treatments to patients and families with neurocognitive disorders must rely on up-to-date resources to bridge this gap.

This part of *Gabbard's Treatments of Psychiatric Disorders*, 5th Edition, is designed for this purpose. Each chapter focuses squarely on available and emerging treatments for five of the highly prevalent and severely disabling neurocognitive disorders. The chapter authors and editors strived to limit consideration of current and evolving issues in diagnosis to only those necessary to frame treatment considerations. Part XI begins, in Chapter 63, "Delirium," with a concise review of the nonpharmacological and pharma-

cological treatments of delirium by José Maldonado. In the following chapter, Chapter 64, "Neurocognitive Disorder Due to Alzheimer's Disease," the distinguished geriatric neuropsychiatrists Christopher Marano, Peter Rabins, and Constantine Lyketsos describe the treatment of cognitive and neuropsychiatric symptoms of neurocognitive disorder due to Alzheimer's disease. The authors emphasize integrating environmental, behavioral, educational, supportive, and pharmacological interventions in the service of comprehensive care, and provide a framework for clinical management that informs the care of all neurocognitive disorders. In Chapter 65, "Frontotemoral Neurocognitive Disorder," the behavioral neurologists Geoffrey Kerchner and Michael Rosenbloom review the nonpharmacological, pharmacological, and emerging treatments of frontotemporal neurocognitive disorder. In Chapter 66, "Vascular Neurocognitive Disorder," Gustavo Román, a pioneer in the diagnosis and treatment of vascular cognitive impairments, presents a primer on subtypes of vascular neurocognitive disorder, pharmacological treatments of vascular cognitive impairments, and cognitively relevant modification strategies for cerebrovascular disease risk factors. Part XI closes with Chapter 67, "Neurocognitive Disorder Due to Parkinson's Disease," a succinct discussion of the pharmacotherapy and cognitive rehabilitation of neurocognitive disorder due to Parkinson's disease, as well as the future of treatments for this condition, by Laura Marsh and Michele York, two renown experts in the nonmotor aspects of Parkinson's disease.

Readers of the chapters in this part will inevitably gain an appreciation for the complexities of caring for persons with neurocognitive disorders, as well as an understanding of the need for the development of treatments with disease-modifying properties. At the same time, readers will be positioned to provide evidence-informed treatments for these conditions and to improve the lives of the ever-increasing number of patients and families affected by neurocognitive disorders.

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CHAPTER 63

Delirium

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Delirium is common in general hospital settings and negatively affects the care and outcomes of medically ill patients. Interdisciplinary collaboration on delirium prevention, recognition, and treatment is a core component of effective management (Maldonado 2011). The medical management of delirium begins with the implementation of prevention measures. Administration of assessment scales or diagnostic interviews facilitates timely recognition of delirium and provides opportunities to prevent and treat this condition in a manner that minimizes its adverse long-term consequences (Maldonado 2008) (Box 63–1).

Box 63–1. DSM-5 Diagnostic Criteria for Delirium

A. A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
D. The disturbances in Criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Specify whether:

Substance intoxication delirium: This diagnosis should be made instead of substance intoxication when the symptoms in Criteria A and C predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Coding note: The ICD-9-CM and ICD-10-CM codes for the [specific substance] intoxication delirium are indicated in the table below. Note that the ICD-10-CM code depends on whether or not there is a comorbid substance use disorder present for the same class of substance. If a mild substance use disorder is comorbid with the substance intoxication delirium, the 4th position character is "1," and the clinician should record "mild [substance] use disorder" before the substance intoxication delirium (e.g., "mild cocaine use disorder with cocaine intoxication delirium"). If a moderate or severe substance use disorder is comorbid with the substance intoxication delirium, the 4th position character is "2," and the clinician should record "moderate [substance] use disorder" or "severe [substance] use disorder," depending on the severity of the comorbid substance use disorder. If there is no comorbid substance use disorder (e.g., after a one-time heavy use of the substance), then the 4th position character is "9," and the clinician should record only the substance intoxication delirium.

		ICD-10-CM		
	ICD-9-CM	With use disorder, mild	With use disorder, moderate or severe	Without use disorder
Alcohol	291.0	F10.121	F10.221	F10.921
Cannabis	292.81	F12.121	F12.221	F12.921
Phencyclidine	292.81	F16.121	F16.221	F16.921
Other hallucinogen	292.81	F16.121	F16.221	F16.921
Inhalant	292.81	F18.121	F18.221	F18.921
Opioid	292.81	F11.121	F11.221	F11.921
Sedative, hypnotic, or anxiolytic	292.81	F13.121	F13.221	F13.921
Amphetamine (or other stimulant)	292.81	F15.121	F15.221	F15.921
Cocaine	292.81	F14.121	F14.221	F14.921
Other (or unknown) substance	292.81	F19.121	F19.221	F19.921

Substance withdrawal delirium: This diagnosis should be made instead of substance withdrawal when the symptoms in Criteria A and C predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Code [specific substance] withdrawal delirium: **291.0 (F10.231)** alcohol; **292.0 (F11.23)** opioid; **292.0 (F13.231)** sedative, hypnotic, or anxiolytic; **292.0 (F19.231)** other (or unknown) substance/medication.

Medication-induced delirium: This diagnosis applies when the symptoms in Criteria A and C arise as a side effect of a medication taken as prescribed.

Coding note: The ICD-9-CM code for [specific medication]-induced delirium is **292.81.** The ICD-10-CM code depends on the type of medication. If the medication is an opioid taken as prescribed, the code is **F11.921.** If the medication is a sedative, hypnotic, or anxiolytic taken as prescribed, the code is **F13.921.** If the medication is an amphetamine-type or other stimulant taken as prescribed, the code is **F15.921.** For medications that do not fit into any of the classes (e.g., dexametha-

sone) and in cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the code is **F19.921.**

293.0 (F05) Delirium due to another medical condition: There is evidence from the history, physical examination, or laboratory findings that the disturbance is attributable to the physiological consequences of another medical condition.

Coding note: Include the name of the other medical condition in the name of the delirium (e.g., 293.0 [F05] delirium due to hepatic encephalopathy). The other medical condition should also be coded and listed separately immediately before the delirium due to another medical condition (e.g., 572.2 [K72.90] hepatic encephalopathy; 293.0 [F05] delirium due to hepatic encephalopathy).

293.0 (F05) Delirium due to multiple etiologies: There is evidence from the history, physical examination, or laboratory findings that the delirium has more than one etiology (e.g., more than one etiological medical condition; another medical condition plus substance intoxication or medication side effect).

Coding note: Use multiple separate codes reflecting specific delirium etiologies (e.g., 572.2 [K72.90] hepatic encephalopathy, 293.0 [F05] delirium due to hepatic failure; 291.0 [F10.231] alcohol withdrawal delirium). Note that the etiological medical condition both appears as a separate code that precedes the delirium code and is substituted into the delirium due to another medical condition rubric.

Specify if:

Acute: Lasting a few hours or days.

Persistent: Lasting weeks or months.

Specify if:

Hyperactive: The individual has a hyperactive level of psychomotor activity that may be accompanied by mood lability, agitation, and/or refusal to cooperate with medical care.

Hypoactive: The individual has a hypoactive level of psychomotor activity that may be accompanied by sluggishness and lethargy that approaches stupor.

Mixed level of activity: The individual has a normal level of psychomotor activity even though attention and awareness are disturbed. Also includes individuals whose activity level rapidly fluctuates.

If delirium develops despite these measures, treatment aims to optimize patient comfort, minimize pain, prevent or treat delirium, restore an adequate sleep-wake pattern, begin physical mobilization as early as possible, improve cognitive recovery, and return the patient to clinical and functional baseline as quickly as possible. Three goals are used to organize efforts in the service of these aims: management of the behavioral and psychiatric manifestations and symptoms to prevent the patient from self-harm or harming of others, treatment or correction of underlying medical problems and potential reversible factors, and attempts to correct the cerebral neurochemical derangement producing the clinical symptoms of delirium. These goals are met through a combination of nonpharmacological and pharmacological interventions.

Nonpharmacological Treatments

The Hospital Elder Life Program (Inouye et al. 2000) provides guidance on the interdisciplinary team identification and management of risk factors for cognitive decline in the elderly, including cognitive

impairment, sleep deprivation, immobility, dehydration, and visual or hearing impairment. This approach is the foundation for the U.K.'s National Institute for Health and Clinical Excellence (NICE) guidelines for the prevention of delirium in elderly at-risk patients (O'Mahony et al. 2011), which can effectively prevent delirium among postoperative elderly orthopedic patients (Holroyd-Leduc et al. 2010). There remains a need for the further development of these and related measures, however, because they are inconsistently effective for delirium prevention (Gagnon et al. 2012) and their effects on delirium severity and duration, fall risk, length of hospital stay, discharge location, postdischarge dependency, and mortality rate are suboptimal (Holroyd-Leduc et al. 2010).

When delirium develops, nonpharmacological management emphasizes the elimination or reduction of medical, sensory, and environmental factors that may contribute to delirium (Maldonado 2011). Adequate nutrition, hydration, and electrolyte balance must be ensured. Nonessential immobilizing devices (i.e., restraints) and lines should be eliminated. If immobilizing devices must be used to prevent harm to self and others, then brief and behavior-targeted application followed by prompt removal when the target symptoms abate is recommended. Prescribed medications need to be reviewed, and agents that may contribute to delirium should be discontinued, especially those that augment cerebral γ-aminobutryic acid function (e.g., benzodiazepines) and/or diminish cerebral acetylcholinergic function (i.e., directly or indirectly anticholinergic medications). Identifying pain and providing adequate analgesia may reduce delirium-related agitation; however, opioid medications should be avoided because they may compromise arousal and behavior.

Correcting sensory deficits (i.e., poor vision or poor hearing) may improve engagement with the environment, especially when coupled with adequate intellectual stimulation during waking hours (except for television, which should be avoided). Using nonpharmacological sleep protocols facilitates normalization of sleep-wake cycles. Among endotracheally intubated and sedated patients, implementing a "daily awakening" protocol (i.e., periodically decreasing sedation) provides opportunities for reorientation and physical and occupational therapy, which appear to shorten duration of delirium (Needham and Korupolu 2010; Schweickert et al. 2009).

Pharmacological Treatments

The goals of pharmacological treatment of delirium are to reduce the behavioral and psychiatric manifestations and symptoms through correction of delirium-inducing neurotransmitters and to reduce the risk of self-harm and/or harming of others. There are no medications approved by the U.S. Food and Drug Administration (FDA) for the prevention or treatment of delirium, so all of the pharmacotherapies discussed represent "off-label" uses of medications.

Antipsychotics

Elevation in cerebral dopamine levels has been associated with all forms of delirium, including hyperactive (or agitated) and hypoactive types. Accordingly, antipsychotic medications (which antagonize and/or indirectly modulate cerebral dopamine function) are useful treatments for agitated and mixed-type deliria in

general, and especially critical illness–related delirium, as well as hypoactive delirium (Lonergan et al. 2007).

Typical prophylaxis antipsychotics (also known as second-generation antipsychotics, or SGAs) afford a 50% decrease in the relative risk of postoperative delirium incidence, intensity, and duration (Teslyar et al. 2013) and support brief, time-limited perioperative use of prophylactic dopamine antagonists—including first-generation antipsychotics (FGAs) and SGAs—to prevent postoperative delirium in the elderly (Zhang et al. 2013).

Intravenous haloperidol is recommended as the medication of choice for the management of critically ill patients with delirium by a number of national organizations, including NICE (National Institute for Health and Clinical Excellence 2010), the American Psychiatric Association (American Psychiatric Association 1999), and the Society of Critical Care Medicine (Jacobi et al. 2002). Despite these recommendations, clinicians should be mindful that the FDA issued a black box warning for intravenous (as well as high-dose) haloperidol in light of an associated risk for torsade de pointes and QT prolongation (U.S. Food and Drug Administration 2007).

SGAs also are used commonly to treat delirium and appear to reduce delirium-related agitation, shorten duration of delirium, increase likelihood of discharge to home (rather than to a long-term care facility), lower the need for adjunctive haloperidol, and produce few extrapyramidal side effects (Breitbart et al. 1996; Hawkins et al. 2013). Studies directly comparing the efficacy of haloperidol with that of SGAs demonstrate no between-treatment differences and similar rates of adverse effects (Lonergan et al. 2007). Risperidone is the most studied SGA for delirium, and it appears to be 80%–85% effective in treating the behavioral disturbances of delirium at doses of 0.5–4 mg/day (Ozbolt et al. 2008). Similarly, olanzapine is approximately 70%–76% effective in treating the behavioral manifestations of delirium at mean doses of 2.5–11.6 mg/day. There also is evidence for quetiapine (Hawkins et al. 2013), ziprasidone (Lonergan et al. 2007), and aripiprazole (Boettger and Breitbart 2011) in delirium management, all of which appear to be useful for this purpose.

A recent review (Meagher et al. 2013) of 28 studies of delirium treatment using antipsychotic agents reached four main conclusions. First, approximately 75% of patients with delirium who receive short-term treatment with low-dose antipsychotics respond favorably to this treatment. Second, these response rates are relatively consistent across different patient groups and treatment settings. Third, the evidence does not suggest that delirium subtypes differ significantly with respect to antipsychotic treatment response rates. Fourth, there are no significant differences in the efficacy of haloperidol and atypical antipsychotics in the treatment of delirium.

The FGAs and SGAs used for delirium are associated with similar rates of adverse drug events. In general, these agents are not used long term, and therefore, treatment-associated weight gain; dyslipidemia; high blood pressure; and long-term risks of cardiovascular disease, diabetes, and metabolic syndrome are less relevant concerns except in patients with preexisting illnesses of these types. Because all antipsychotics may prolong the QTc interval, they must be administered with caution, if at all, to patients concurrently taking other QTc interval–prolonging medications and/or inhibitors of the cytochrome P450 CPY3A4 pathway. Before and during the

use of continuous antipsychotic management, 12-lead electrocardiogram, measurement and monitoring of the QTc interval, and correction of electrolytes (especially potassium and magnesium) are recommended. Antipsychotic use must be discontinued if QTc increases by greater than 25% of pretreatment baseline or to greater than 500 milliseconds.

Sedatives

Sedatives and opioids may contribute to the development of delirium by interfering with physiological sleep patterns; interfering with central cholinergic function; increasing compensatory up-regulation of *N*-methyl-D-aspartate (NMDA), kainate receptors, and calcium channels; disrupting the circadian rhythm of melatonin release; disrupting thalamic gating function; and producing central nervous system dependence and withdrawal. Many patients receiving care in general medical settings are treated with sedatives, especially those in critical care settings and/or on mechanical ventilators. Therefore, avoiding or using alternatives to sedating medications may decrease the risk of developing sedative-induced delirium in these patients (Maldonado 2008).

Dexmedetomidine, an α_2-adrenergic receptor agonist, is an alternative to conventional sedation, and its use decreases the incidence of postoperative delirium and shortens the duration of delirium in comparison with treatment with midazolam or propofol (Maldonado et al. 2009; Pandharipande et al. 2007; Reade et al. 2009; Riker et al. 2009). When used adjunctively with propofol, dexmedetomidine reduced the duration of delirium, hastened safe extubation, produced less systolic hypotension, and reduced the need for adjunctive norepinephrine when compared with adjunctive treatment with morphine-treated patients (Shehabi et al. 2009). Clonidine, another α_2-adrenergic receptor agonist, also reduces the severity of delirium, improves respiratory function, shortens ventilator weaning duration, and reduces intensive care unit lengths of stay (Rubino et al. 2010). These observations suggest a potentially useful role for α_2-adrenergic receptor agonists, and particularly dexmedetomidine, in delirium prevention and management (Zhang et al. 2013).

Uncompetitive *N*-Methyl-D-Aspartate Antagonists

Amantadine and memantine are uncompetitive NMDA receptor antagonists that prevent glutamate-mediated excess calcium influx into neurons, reduce the release of pro-inflammatory factors from activated microglia, induce expression of neurotrophic factors (e.g., glial cell line–derived neurotrophic factor), and limit oxidative injury and excitatory amino acid–mediated neurotoxicity (Giacino and Whyte 2003; Kutzing et al. 2012; Ossola et al. 2011; Zaja-Milatovic et al. 2009). The use of amantadine and memantine in syndromes associated with excess glutamatergic activity and associated cognitive dysfunction, including delirium, therefore may be neurobiologically rational. Consistent with this suggestion, amantadine has been shown to accelerate the rate of recovery among persons with disorders of consciousness (i.e., vegetative state or minimally conscious state) during the subacute period following severe traumatic brain injury in humans (Giacino et al. 2012). However, the use of these agents for the treatment of delirium more specifically has not been investigated.

Anticonvulsants

Valproic acid is used routinely as an adjunct to conventional medications (i.e.,

antipsychotics) in the treatment of agitated delirious patients who either fail to respond to or are intolerant of conventional medications. However, there is little published evidence supporting this practice (Bourgeois et al. 2005; Lum et al. 2006). Nonetheless, the availability of intravenous valproate and elixir forms of this medication allows for rapid administration and symptom management in patients unable or unwilling to take oral medications. When this medication is used, liver function tests, bilirubin, platelet count, and amylase must be monitored closely during treatment.

Although not a treatment of delirium, gabapentin also may be useful as an alternative to opioids for the treatment of postoperative pain and reduces the development of delirium in that context (Leung et al. 2006). Further studies are needed to evaluate the role of this and other anticonvulsants in the prevention and treatment of delirium (Campbell et al. 2009).

Acetylcholinesterase Inhibitors

A Cochrane Database review concluded that the treatment of delirium with acetylcholinesterase inhibitors is of uncertain benefit (Overshott et al. 2008) at best and casts doubt on the usefulness of this class of medication for delirium prevention.

Rivastigmine

A recent double-blind placebo-controlled study of rivastigmine as an adjunct to the treatment of delirium with haloperidol was halted because of an unexpectedly higher mortality rate in the rivastigmine-treated group (van Eijk et al. 2010), raising questions about the safety of this medication combination. However, this observation requires cautious interpretation: The study used a rapid rivastigmine titration protocol that deviates substantially from the manner in which the medication is used in routine clinical practice, and this approach may have increased the risk of adverse events related to rivastigmine. The causes of death in this study were also heterogeneous, and some may not have been treatment related.

Physostigmine

An exception to the use of acetylcholinesterase inhibitors in the treatment of delirium is anticholinergic delirium, for which physostigmine, a short-acting acetylcholinesterase inhibitor that increases synaptic acetylcholine concentrations, carries an FDA-approved indication. This agent is consistently effective and usually well tolerated (Burns et al. 2000; Schneir et al. 2003). Given its safety profile and effectiveness, physostigmine should be considered when a delirious patient exhibits on examination signs of a central anticholinergic state (i.e., combined symptoms of confusion, hyperthermia, sinus tachycardia, mydriasis, dry mouth, dry eyes, dry skin, and flushing) and/or when it is known that the patient's altered mental status is due to use of known anticholinergic substances (e.g., diphenhydramine). Prolonged PR interval (>200 milliseconds) or QRS interval (>100 milliseconds and not related to bundle branch block) on electrocardiogram is a relative contraindication to treatment with physostigmine. Clinicians should review the FDA product labeling for additional cautions and contraindications and consult a critical care specialist before administering this medication.

Melatonin and Related Medications

Melatonin plays an important role in the regulation of circadian rhythm and main-

tenance of a physiological, well-regulated sleep-wake pattern (Brzezinski 1997). Disturbances of melatonin release and function may contribute to delirium (De Rooij 2013; Maldonado 2008). Case reports suggest that low-dose melatonin or ramelteon (a melatonin agonist) may contribute usefully to the prevention of postoperative delirium and to the treatment of severe postoperative delirium unresponsive to antipsychotics or benzodiazepines (De Rooij 2013). Melatonin also may be useful for the treatment of so-called sundowning among persons with dementia (de Jonghe et al. 2010), consistent with the framing of this condition as a form of delirium.

Other Medications

Ondansetron, a selective serotonin type-3 receptor antagonist, may be a useful medication for the treatment of postoperative delirium (Bayindir et al. 2001), consistent with the hypothesized role of serotonergic disturbances in the pathogenesis of delirium (Maldonado 2008; Tagarakis et al. 2012). In light of the antithrombotic, anti-inflammatory, and immunomodulatory properties of statins, preoperative administration has been suggested as a possible postoperative delirium prevention strategy for elderly patients (Katznelson et al. 2009). Further investigation of these and other treatments for delirium derived from the known pathophysiology of this condition may yield alternatives to presently available delirium prevention and treatment strategies.

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CHAPTER 64

Neurocognitive Disorder Due to Alzheimer's Disease

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Alzheimer's disease (AD) is a slowly progressive neurocognitive disorder with a preclinical phase in which the individual may be asymptomatic for many years. This preclinical phase is followed by a period, generally termed mild cognitive impairment (MCI), of impaired cognition and possible neuropsychiatric symptoms without functional deficit. Eventually, individuals with AD develop a dementia or neurocognitive syndrome with cognitive deficits, functional decline, and neuropsychiatric symptoms. The DSM-5 criteria for major or mild neurocognitive disorder due to AD are listed in Box 64–1 (American Psychiatric Association 2013).

There currently are no disease-modifying treatments for the underlying pathophysiology of AD or to prevent the transition from preclinical AD to MCI or from MCI to dementia. This is an active area of research, however, guided by newly emerging AD biomarkers, and clinicians are encouraged to stay abreast of emerging disease-modifying treatment (Karran et al. 2011; Lyketsos et al. 2008).

Box 64–1. DSM-5 Diagnostic Criteria for Neurocognitive Disorder Due to Alzheimer's Disease

A. The criteria are met for major or mild neurocognitive disorder.
B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired).
C. Criteria are met for either probable or possible Alzheimer's disease as follows:

For major neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if either of the following is present; otherwise, **possible Alzheimer's disease** should be diagnosed.

1. Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing.
2. All three of the following are present:
   a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).
   b. Steadily progressive, gradual decline in cognition, without extended plateaus.
   c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).

For mild neurocognitive disorder:

Probable Alzheimer's disease is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history.

Possible Alzheimer's disease is diagnosed if there is no evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history, and all three of the following are present:

1. Clear evidence of decline in memory and learning.
2. Steadily progressive, gradual decline in cognition, without extended plateaus.
3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline).

D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

Coding note: For probable major neurocognitive disorder due to Alzheimer's disease, with behavioral disturbance, code first **331.0 (G30.9)** Alzheimer's disease, followed by **294.11 (F02.81)** major neurocognitive disorder due to Alzheimer's disease. For probable major neurocognitive disorder due to Alzheimer's disease, without behavioral disturbance, code first **331.0 (G30.9)** Alzheimer's disease, followed by **294.10 (F02.80)** major neurocognitive disorder due to Alzheimer's disease, without behavioral disturbance.

For possible major neurocognitive disorder due to Alzheimer's disease, code **331.9 (G31.9)** possible major neurocognitive disorder due to Alzheimer's disease. (**Note:** Do *not* use the additional code for Alzheimer's disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

For mild neurocognitive disorder due to Alzheimer's disease, code **331.83 (G31.84).** (**Note:** Do *not* use the additional code for Alzheimer's disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

In the absence of such treatments, the primary goals of dementia care currently are maximization of quality of life through treatment of cognitive, emotional, and behavioral symptoms; delay of disability and institutionalization; provision of comfort; and preservation of dignity—goals that also are applied to work with and support a patient's caregiver (Rabins et al. 2006). Given the lack of disease-modifying treatments and the limited effectiveness of pharmacological treatments for both the cognitive and neuropsychiatric symptoms of AD, the most effective current treatments are environmental or behavioral. Therefore, the practicing psychiatrist must approach care of patients with dementia in a comprehen-

sive manner (i.e., one that entails more than pharmacotherapy) and is positioned uniquely to do so.

Treating Cognitive Impairments

Prior to the initiation of pharmacological therapy for AD symptoms, the doses of medications that impair cognition (e.g., anticholinergics, opioid analgesics, benzodiazepines) need to be eliminated or minimized. Additionally, the clinician should review all available treatments (Table 64–1) and establish realistic expectations regarding their effects on cognition and other symptoms of dementia.

Acetylcholinesterase Inhibitors

The cholinergic hypothesis of AD suggests that degeneration of cholinergic neurons in the basal forebrain results in decreased cholinergic transmission to the cerebral cortex and other areas of the brain (Francis et al. 1999); this, in turn, contributes to cognitive dysfunction. Acetylcholinesterase inhibitors reversibly inhibit the activity of acetylcholinesterase, the enzyme responsible for synaptic metabolism of acetylcholine; their administration thereby increases levels of synaptic acetylcholine. The acetylcholinesterase inhibitors used in clinical practice are donepezil, galantamine, and rivastigmine, all of which are approved by the U.S. Food and Drug Administration (FDA) for the treatment of mild to moderate AD. Donepezil also is approved for the treatment of severe AD.

Acetylcholinesterase inhibitors produce modest cognitive improvements at best (Birks 2006). However, some patients respond more robustly than others to acetylcholinesterase inhibitors, and predictors of clinical improvement response remain elusive. Moreover, stabilization of cognition—rather than improvement—is a more realistic treatment goal for most patients. In clinical practice, establishing a pretreatment baseline with a measure such as the Mini-Mental State Examination (MMSE; Folstein et al. 1975) and evaluating the effects of treatment through periodic reevaluation with this measure is recommended. If a patient tolerates treatment with an acetylcholinesterase inhibitor, then a therapeutic trial of at least 6 months is appropriate.

Despite their slight mechanistic differences, the presently available acetylcholinesterase inhibitors are of comparable efficacy (Birks 2006). Treatment selection therefore is a matter of patient and caregiver preference and clinician judgment, which may be informed by ease-of-use and tolerability considerations. All of the acetylcholinesterase inhibitors are available in oral forms, and most have once-daily administration options (including a transdermal route for rivastigmine). Donepezil is available in an orally disintegrating tablet for patients with swallowing difficulties, and transdermal administration of rivastigmine permits administration to patients who are unable to take oral medications.

An uncommon but potentially serious adverse effect of treatment is bradycardia (Park-Wyllie et al. 2009), which may occur in patients with and without known underlying cardiac conduction abnormalities. When treatment-related bradycardia requires hospitalization, it secondarily increases the risk of syncope, pacemaker insertion, and hip fracture (Gill et al. 2009). The most common adverse effects of acetylcholinesterase inhibitors are gastrointestinal in nature,

TABLE 64–1. Pharmacological treatments for the cognitive symptoms of Alzheimer's disease

Drug	Mechanism	Initial dose	Target dose	Comments
Donepezil	AChEI	5 mg/day	10 mg/day	Oral dissolving tablet, once-daily dosing, and dose titration protocol simplify use; use of 23 mg daily dose is controversial.
Galantamine	AChEI and allosteric nicotinic receptor modulation	4 mg bid (immediate release) or 8 mg/day (extended release)	8–12 mg bid (immediate release) or 16–24 mg/day (extended release)	Bradycardia is a reported problem but is rarely severe enough to require treatment discontinuation.
Rivastigmine	AChEI and BuChEI	1.5 mg bid (oral) or 4.6 mg/day (transdermal)	3–6 mg bid (oral) or 9.5 mg/day (transdermal)	Nonhepatic metabolism; transdermal administration decreases gastrointestinal side effects.
Memantine	NMDA receptor antagonism	5 mg/day	10 mg bid	Dose adjustment is required for decreased creatinine clearance; may be administered in a single daily dose if necessary.

Note. AChEI = acetylcholinesterase inhibition; BuChEI = butyrylcholinesterase inhibition; NMDA = uncompetitive *N*-methyl-D-aspartate.

including nausea, vomiting, and diarrhea. Transdermal administration of rivastigmine appears to reduce the risk of gastrointestinal side effects when compared to oral rivastigmine (Winblad et al. 2007), and high-dose donepezil (i.e., 23 mg/day) is associated with reduced treatment tolerability due to these and other adverse events (Farlow et al. 2010).

Switching Between Acetylcholinesterase Inhibitors

Whether and/or when to switch between acetylcholinesterase inhibitors are common clinical questions, and there is limited evidence with which to develop informed answers (Massoud et al. 2011). For primary lack of effectiveness, switching may be started on the day following the last administration of the ineffective medication. Switching for treatment intolerance should be made only after complete resolution of side effects following discontinuation of the initial agent. In general, switching treatment from one acetylcholinesterase inhibitor to another due to perceived loss of benefit following years of treatment is not recommended.

Discontinuing Treatment With Acetylcholinesterase Inhibitors

Another common clinical dilemma is determining whether and/or when to stop treatment with an acetylcholinesterase inhibitor. Discontinuation is a reasonable option in late dementia, especially when the burden of side effects outweighs perceived treatment benefits. However, treatment discontinuation may result in worsening cognitive and behavioral symptoms (Howard et al. 2012). The decision to discontinue treatment with an acetylcholinesterase inhibitor—much like treatment selection and initiation—is therefore a matter of patient and caregiver preference and clinician judgment.

Memantine

Memantine is an uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist approved for the treatment of moderate to severe dementia due to AD. The effects of memantine on cognition are similar to those of the cholinesterase inhibitors. Memantine is generally well tolerated, with adverse events similar to those of placebo in clinical trials. Twice-daily dosing is recommended, although its long half-life allows once-daily dosing if necessary (Jones et al. 2007). Given memantine's renal excretion, the maximum memantine dosage is 5 mg bid for creatinine clearances between 5 and 29 mL/min.

Cholinesterase inhibitors and memantine often are administered concurrently, although limited evidence supports this practice. A recent systematic review suggests a small cognitive but not functional benefit from combination therapy (Farrimond et al. 2012), whereas a 1-year clinical trial demonstrated no benefit of donepezil plus memantine over donepezil alone in patients with moderate to severe AD (Howard et al. 2012). Nonetheless, concurrent treatment with a cholinesterase inhibitor and memantine is a common and accepted practice in most clinical settings.

Treating Neuropsychiatric Symptoms

Although cognitive and functional declines are hallmarks of AD, neuropsychiatric symptoms (i.e., emotional and

behavioral disturbances) are nearly universal features of this condition (Steinberg et al. 2008). Typical neuropsychiatric symptoms of AD include delusions, hallucinations, agitation, depression, anxiety, elation or euphoria, apathy or indifference, disinhibition, irritability or lability, aberrant motor behaviors (e.g., pacing, wandering, perseveration), sleep disturbances, and changes in appetite and eating (Cummings et al. 1994). Neuropsychiatric symptoms are associated with worse quality of life, greater disability, accelerated cognitive or functional decline, greater caregiver burden, earlier institutionalization, and accelerated mortality (Rabins et al. 2006).

The first step in treating AD-related neuropsychiatric symptoms is a thorough diagnostic evaluation to rule out other causes of cognitive impairment, neuropsychiatric disturbance, and functional disability (e.g., delirium, psychiatric disorders, substance use disorders, neurological disorders). The next step is to carefully characterize the neuropsychiatric symptoms requiring treatment using standardized, validated, reliable, and repeatable assessments.

After a thorough assessment, nonpharmacological management strategies are the first component of treatment. An in-depth review of these strategies is beyond the scope of this chapter and may be found elsewhere (Brodaty and Arasaratnam 2012; Gitlin et al. 2012). Briefly, these strategies call for behavior analysis and modification of antecedents (including environmental and caregiver factors), behaviors, and consequences that may be contributing to the expression of the target symptom.

If nonpharmacological approaches do not provide the desired level of improvement in neuropsychiatric symptoms, or if there is acute danger, or if there is an identifiable psychiatric syndrome, the next step is to decide whether to treat the patient with medication. No medications have been specifically approved by the FDA for the treatment of AD-related neuropsychiatric symptoms. Nonetheless, the practical indications for medications are neuropsychiatric symptoms that impair the patient's quality of life or function, adversely affect the caregiver's ability to care for the patient, place the patient or others at risk of harm, and/or disrupt the care environment to such a degree that others are experiencing adverse outcomes.

Acetylcholinesterase Inhibitors and Memantine

As a class, acetylcholinesterase inhibitors may delay the emergence of neuropsychiatric symptoms by approximately 12–18 months. However, the effects of these agents on neuropsychiatric symptoms are modest and inconsistently reported (Wynn and Cummings 2004). Acetylcholinesterase inhibitors do not appear to be effective treatments of AD-related agitation (Howard et al. 2007). Some evidence suggests that memantine may reduce the development of agitation among patients with AD, but it does not appear to reduce agitation already present prior to treatment with this agent (McShane et al. 2006).

Antipsychotics

Antipsychotic medications are used to treat AD-related neuropsychiatric symptoms, but they must be used judiciously given their risks. Both conventional and atypical antipsychotics show modest efficacy in some clinical trials of neuropsychiatric symptoms (Ballard and Waite 2006; Schneider et al. 1990, 2006b), and recurrent psychosis or agitation may occur after antipsychotic discontinuation

(Devanand et al. 2012). However, large-scale trials have called into question the overall benefits of antipsychotic medications in this context (Schneider et al. 2006a) and clarified that they are not course-modifying agents (Vigen et al. 2011). Accordingly, if a reasonable empirical trial with an antipsychotic agent in any given patient demonstrates no benefits, that antipsychotic should be discontinued. If treatment does afford benefits, continued use of the ostensibly beneficial medication should be reassessed at regular intervals.

Whenever an antipsychotic medication is used, informed consent should be obtained from an appropriate decision maker (Rabins and Lyketsos 2005). A frank conversation with caregivers regarding the risks and side effects of antipsychotics is required and must include discussion of the FDA black box warning about increased mortality due to cardiovascular or infectious causes in elderly patients with dementia treated with antipsychotic drugs (U.S. Food and Drug Administration 2012)—a risk that may persist after treatment discontinuation (Ballard et al. 2009). This risk appears to be higher for typical than for atypical antipsychotics (Wang et al. 2005): the mortality risk is highest with haloperidol; intermediate with risperidone, olanzapine, aripiprazole, and ziprasidone; and lowest with quetiapine (Huybrechts et al. 2012; Kales et al. 2012). This treatment-associated mortality risk is highest during the early period after treatment initiation and associated with higher doses of antipsychotic medication (Huybrechts et al. 2012; Kales et al. 2012; Wang et al. 2005), and does not generalize to other psychotropic medications (Kales et al. 2007).

When atypical antipsychotics are being used, the recommendation is to start at very low dosages (e.g., quetiapine 12.5–25 mg/day, risperidone 0.25 mg/day, olanzapine 1.25–2.5 mg/day) and closely monitor for side effects, including orthostatic hypotension. Dosing, formulation, and propensity for extrapyramidal symptoms are also considerations, particularly in patients with preexisting parkinsonism.

Anticonvulsants

As an alternative to antipsychotics, valproic acid is sometimes used to treat the agitation of patients with AD. However, multiple negative studies—including a 24-month study in which valproic acid failed to delay emergence of agitation or psychosis, failed to slow cognitive loss, and demonstrated significant toxicity (Tariot et al. 2011)—provide no support for this practice. The evidence for carbamazepine as a treatment for agitation in dementia is more encouraging (Olin et al. 2001); however, the need for hematological parameter monitoring, the potential for blood dyscrasia, and multiple drug-drug interactions limit enthusiasm for the use of carbamazepine in the treatment of persons with AD-related neuropsychiatric disturbances.

Antidepressants

Antidepressant medications also are used to treat AD-related neuropsychiatric symptoms, including depression, anxiety, and agitation. In general, antidepressants are reasonable treatments for depression and anxiety among persons with AD, although expectations regarding their effectiveness should be relatively modest (Banerjee et al. 2011; Rosenberg et al. 2010). Antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), are also reasonable first-line treatments for mild agitation as

a primary symptom and, given their more favorable side-effect and risk profiles, are preferable in this regard to antipsychotics. The available evidence suggests that citalopram and sertraline may be useful for this purpose. Although trazodone also is used to treat AD-related agitation, insufficient evidence is available to support use of this medication for this purpose.

Although antidepressants may be useful treatments for AD-related neuropsychiatric symptoms, the emerging evidence suggests that they should not be regarded as entirely benign treatments. Citalopram demonstrates dose-dependent QT prolongation, which limits maximum dosing in persons older than age 60 years to 20 mg/day (U.S. Food and Drug Administration 2012); therefore, this agent has limited usefulness as a treatment of AD-related neuropsychiatric disturbances. SSRIs and other newer antidepressants also are associated with increased risks of hyponatremia and falls (Coupland et al. 2011). Accordingly, when antidepressants are used, selecting agents without potent anticholinergic properties and with limited potential for drug-drug interactions (e.g., sertraline, citalopram, escitalopram) is recommended. Regardless of the treatment prescribed, careful monitoring (in collaboration with a well-informed caregiver) for treatment effects, side effects, and other adverse events is essential.

Benzodiazepines

The use of benzodiazepines should be limited to emergencies. When use of a benzodiazepine is required to prevent imminent harm, lorazepam 0.25 mg (with repeated doses as necessary) is a reasonable choice given its shorter half-life, serum metabolism, and lack of active metabolites.

Supportive Treatments for Patients and Caregivers

Supportive treatments are paramount in treating persons with AD and their caregivers. At a minimum, these interventions include the provision of education, counseling about diagnosis and prognosis, comfort, and emotional support. Instructions on safe and effective caregiving, problem solving, and crisis intervention are important to provide. Clinicians also need to address safety concerns, including driving (and its eventual restriction), living independently, medication administration, and fall risks. Patients may also benefit from structure, including a safe predictable place to live with support for activities of daily living, assistance with managing medical comorbidities, and assistance with advanced planning and end-of-life decisions. Respite care may also be appropriate to allow attention to the personal needs and wants of the caregiver.

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CHAPTER 65

Frontotemporal Neurocognitive Disorder

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Frontotemporal neurocognitive disorder (FTNCD) represents a spectrum of neurodegenerative diseases that compromise function of frontal brain networks, resulting in cognitive and behavioral deficits (see Box 65–1). More often referred to as *frontotemporal dementia* in the medical literature, FTNCD is a common cause of dementia among patients ages 45–65 years and comprises two sometimes overlapping clinical syndromes: behavioral-variant frontotemporal neurocognitive disorder (Bv-FTNCD) and language-variant frontotemporal neurocognitive disorder (Lv-FTNCD) (Table 65–1). The latter syndrome includes two subtypes: progressive nonfluent aphasia (PNFA) and semantic dementia.

Box 65–1. DSM-5 Diagnostic Criteria for Major or Mild Frontotemporal Neurocognitive Disorder

A. The criteria are met for major or mild neurocognitive disorder.
B. The disturbance has insidious onset and gradual progression.
C. Either (1) or (2):
   1. Behavioral variant:
      a. Three or more of the following behavioral symptoms:
         i. Behavioral disinhibition.
         ii. Apathy or inertia.
         iii. Loss of sympathy or empathy.
         iv. Perseverative, stereotyped or compulsive/ritualistic behavior.
         v. Hyperorality and dietary changes.
      b. Prominent decline in social cognition and/or executive abilities.

2. Language variant:
   a. Prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension.

D. Relative sparing of learning and memory and perceptual-motor function.
E. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

Probable frontotemporal neurocognitive disorder is diagnosed if either of the following is present; otherwise, **possible frontotemporal neurocognitive disorder** should be diagnosed:

1. Evidence of a causative frontotemporal neurocognitive disorder genetic mutation, from either family history or genetic testing.
2. Evidence of disproportionate frontal and/or temporal lobe involvement from neuroimaging.

Possible frontotemporal neurocognitive disorder is diagnosed if there is no evidence of a genetic mutation, and neuroimaging has not been performed.
Coding note: For probable major neurocognitive disorder due to frontotemporal lobar degeneration, with behavioral disturbance, code first **331.19 (G31.09)** frontotemporal disease, followed by **294.11 (F02.81)** probable major neurocognitive disorder due to frontotemporal lobar degeneration, with behavioral disturbance. For probable major neurocognitive disorder due to frontotemporal lobar degeneration, without behavioral disturbance, code first **331.19 (G31.09)** frontotemporal disease, followed by **294.10 (F02.80)** probable major neurocognitive disorder due to frontotemporal lobar degeneration, without behavioral disturbance.
For possible major neurocognitive disorder due to frontotemporal lobar degeneration, code **331.9 (G31.9)** possible major neurocognitive disorder due to frontotemporal lobar degeneration. (**Note:** Do *not* use the additional code for frontotemporal disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)
For mild neurocognitive disorder due to frontotemporal lobar degeneration, code **331.83 (G31.84).** (**Note:** Do *not* use the additional code for frontotemporal disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

FTNCD involves a variety of largely nonoverlapping neuropathological patterns that are distinct from those observed among persons with Alzheimer's disease (AD). These frontotemporal lobar degeneration (FTLD) pathological subtypes include diseases that are characterized by aggregation of one of three proteins in affected frontal or temporal areas of the cerebral cortex: tau, transactive response DNA-binding protein (TDP-43), and fused-in-sarcoma (FUS). Other less common pathologies have been described. Clinical symptomatology may provide clues about the underlying FTLD subtype, but there are no strict associations between Bv-FTNCD or Lv-FTNCD and a particular histopathology.

There are two general approaches to treatment of FTNCD: disease modification and symptomatic management. Disease-modifying therapies target pathogenic molecules and thereby alter, slow, or arrest the disease process. Unfortunately, no disease-modifying therapies are available for persons with FTNCD at this time. Symptomatic management attempts to control disease man-

TABLE 65–1. Clinical features of behavioral-variant frontotemporal neurocognitive disorder (Bv-FTNCD) and language-variant frontotemporal neurocognitive disorder (Lv-FTNCD), including progressive nonfluent aphasia (PNFA) and semantic dementia (SD)

Subtype	Symptoms	Cognitive profile	Neuroimaging	Motor findings	Neuropathology
Bv-FTNCD	Behavioral disinhibition, apathy, loss of empathy, repetitive or stereotyped motor behaviors, and hyper orality	Deficits in attention, working memory, set shifting, mental flexibility, response inhibition, and abstract reasoning, with relative preservation of memory and visuospatial function	Right hemispheric frontal and/or anterior temporal atrophy, particularly involving the orbitofrontal, insular, and anterior cingulate cortices	Motor neuron disease in 10%–15%; Parkinsonian findings or supranuclear gaze disturbance in others	FTLD-tau, FTLD-TDP, FTLD-FUS, and others
Lv-FTNCD (PNFA)	Slow, effortful, and telegraphic speech; dysarthria; agrammatisms; and occasional asymmetric right foot and hand motor impairment	Agrammatical speech, decreased phonemic fluency, and apraxia of speech, with relative preservation of memory and visuospatial function	Left frontoinsular and perisylvian atrophy	Asymmetric Parkinsonian signs, apraxia, focal dystonia, myoclonus, alien limb phenomenon, supranuclear gaze disturbance, axial rigidity, and postural instability	FTLD-tau in most cases
Lv-FTNCD (SD)	Decreased object naming and single word comprehension	Impaired naming, surface dyslexia, and prosopagnosia, with relative preservation of mem-	Asymmetric anterior and lateral temporal atrophy, usually left	Less common than in other FTNCD subtypes	FTLD-TDP in most cases

ifestations alone, and it is the only approach to FTNCD currently available.

Nonpharmacological Treatments

Nonpharmacological approaches are the first-line interventions for persons with FTNCD and their caregivers. Interventions of these types include counseling and education, provision of useful stimulation and activity, safety planning, and advance care planning.

Counseling and Education

FTNCD affects not only the diagnosed individual but also his or her family and caregivers. Delivering this diagnosis should be accompanied by a formal family meeting where questions related to diagnosis, prognosis, and treatment can be addressed by the health care professional. Referral to community resources such as the Association for Frontotemporal Dementias and/or local chapters of the Alzheimer's Association may be helpful to reinforce the diagnosis and provide access to supportive resources. Caregiver burden associated with FTNCD is greater than that associated with AD (de Vugt et al. 2006; Wong et al. 2012), and providing access to regional caregiver support groups is an essential element of comprehensive care.

The neurodegenerative process of FTNCD fundamentally compromises neural systems required for contextually appropriate behaviors, the ability to use recently learned declarative information, and functional independence. Caregivers therefore will need to learn to tolerate at least some level of odd behaviors in the person with FTNCD, to develop compensatory strategies for cognitive and social deficits, and to modify the environment to cope with new caregiving realities. When social disinhibition due to FTNCD leads to social isolation of the family unit, encouraging patients and families to develop a set of places in which the patient is well known and welcome and where there are limited numbers of other people may provide opportunities for social participation (Merrilees et al. 2010). Families are encouraged to carry a small business-size card explaining the patient's diagnosis and to offer it to new individuals in the environment. When agitation develops in persons with FTNCD, teaching caregivers to identify and avoid triggers may reduce the likelihood of agitation episodes (Merrilees et al. 2010). When such episodes occur, teaching caregivers to remain calm, to not escalate the situation, and to redirect the patient may be useful.

In light of the potentially heritable nature of some types of FTNCD, genetic counseling is encouraged. A certified genetics counselor should be responsible for offering such services and offering guidance on the advisability of counseling and the implications of testing results.

Stimulation and Activity

Moderate physical activity can positively impact mood, sleep, functional ability, and cognition (Baker et al. 2010; Williams and Tappen 2007). Beneficial activities are aerobic in nature and should be engaged in at least 3 times per week. The effects of physical exercise on cognition include executive function (Colcombe and Kramer 2003), which is of particular relevance to patients with Bv-FTNCD.

Patients with Lv-FTNCD, especially PNFA, may benefit from a course of speech therapy to optimize expressive language. These sessions can also be used to familiarize patients with a speech assist device. Electronic device programs

with preprogrammed phrases and voice simulation also may provide useful alternative means of communication for patients with PNFA.

Motor manifestations of FTNCD include symptoms of motor neuron disease (e.g., dysphagia, dysarthria, limb weakness, loss of dexterity, respiratory weakness, and impaired swallowing) and Parkinsonism (e.g., tremor, rigidity, slowness, or imbalance). Speech, occupational, and physical therapy are recommended to manage these symptoms and to assist patients and caregivers with compensatory strategies that maintain functional independence.

Safety

Home safety evaluation is recommended for patients with FTNCD to avoid potential accidents relating to appliances and wandering behavior (Rabinovici and Miller 2010). Support for medication management is also often necessary and may be implemented by an individual's family or a health care professional (e.g., public health nurse or home care provider). As FTNCD-associated executive dysfunction progresses, transfer of responsibility for cognitively demanding activities such as driving and finances is required (Merrilees et al. 2010).

Advance Care Planning

Consultation with financial advisors and legal counsel and discussion of conservatorship is appropriate, and patients are encouraged to establish durable powers of attorney prior to the loss of capacity to do so. End-of-life treatment options and decisions need to take into account effective pain management and the goals of the individual with dementia via advance directive. Decisions about resuscitation and intubation in case of emergency should ideally be made during the earliest stages of the condition. Clinical providers should refer individuals with FTNCD to advance care planning resources to assure that they have tools and can execute documents that will guide their care when they are no longer capable of doing so.

Pharmacological Treatments

There are no medications approved by the U.S. Food and Drug Administration for the treatment of FTNCD. Nonetheless, medications are commonly prescribed to treat symptoms of FTNCD that interfere with quality of life and safety and also to improve the quality of life of the caregivers of persons with this condition. Typical targets of treatment include behavioral excesses such as social disinhibition (including physically aggressive behaviors), emotional disturbances (e.g., irritability and depressive symptoms), compulsive and perseverative behaviors, and appetitive behaviors (e.g., carbohydrate craving and increased sexual drive), as well as behavioral deficits such as apathy. A thorough diagnostic evaluation and careful characterization of target symptoms is a prerequisite to the prescription of any medication.

Additionally, eliminating or reducing medications that may produce or exacerbate cognitive and noncognitive neuropsychiatric symptoms—including delirium—precedes symptom-targeted pharmacotherapy, except when immediate intervention is needed to maintain the safety of the patient, his or her caregiver, or other persons. In particular, prescription of sedative-hypnotic medications (e.g., benzodiazepines), typical (or first-generation) antipsychotic medications, and anticholinergic medications to persons with FTNCD is discouraged.

Serotonergic Medications

Selective serotonin reuptake inhibitors are widely used to treat a variety of behavioral symptoms in patients with FTNCD (Pasquier et al. 2003), including disinhibition, compulsive behavior, irritability, depressive symptoms, carbohydrate craving, and increased sexual drive. Improvements in these types of behavioral excesses are reported during treatment with fluoxetine (Swartz et al. 1997), sertraline (Anneser et al. 2007; Mendez et al. 2005), paroxetine (Chow and Mendez 2002; Moretti et al. 2003a; Swartz et al. 1997), citalopram (Herrmann et al. 2012), and fluvoxamine (Ikeda et al. 2004). These medications are generally well tolerated and safe. However, citalopram can cause QT prolongation and risk for cardiac arrhythmia, and dosing above 20 mg in elderly patients is discouraged. Trazodone, which also modulates serotonergic function, also may improve these types of symptoms in some patients (Lebert and Pasquier 1999).

Antipsychotic Medications

Antipsychotic medications are also used to treat the behavioral symptoms of FTNCD, especially agitation and disinhibition. Case reports describe symptomatic improvements with risperidone (Curtis and Resch 2000), aripiprazole (Fellgiebel et al. 2007), and olanzapine (Moretti et al. 2003b), providing some very limited support for their use. Importantly, patients with FTNCD may be exceptionally sensitive to the motor side effects of antipsychotic medications, with as many as one-third of patients treated with these medications exhibiting problematic extrapyramidal symptoms that often last weeks after medication discontinuation (Pijnenburg et al. 2003). In addition, antipsychotic medications are associated with a risk of death in elderly patients (Wang et al. 2005). For these reasons, antipsychotic drugs are not recommended for routine use in patients with FTNCD unless dangerous behaviors outweigh the medical risks of treatment and a legally authorized substituted decision maker consents to their administration.

Catecholamine-Augmenting Medications

Dopamine agonists such as selegiline, a monoamine oxidase B inhibitor that slows the metabolism of dopamine, may reduce neuropsychiatric symptoms in FTNCD (Moretti et al. 2002). In part because of the pervasive apathy that occurs among many patients with FTNCD, some clinicians have considered the use of psychostimulants (Dolder et al. 2010), including methylphenidate (Rahman et al. 2006) and dextroamphetamine (Huey et al. 2008). The latter of these medications has been observed to concurrently improve apathy and disinhibition (Huey et al. 2008).

Acetylcholinesterase Inhibitors

In FTNCD, there is a relative preservation of cholinergic neurons in the brain and no a priori reason to expect a benefit from cholinesterase inhibition (Huey et al. 2006). Data regarding the efficacy of acetylcholinesterase inhibitors in FTNCD are mixed and difficult to interpret. Although open-label studies of donepezil and rivastigmine suggested possible cognitive and neuropsychiatric benefits (Lampl et al. 2004; Moretti et al. 2004), a large double-blind study of galantamine demonstrated no benefit on cognition or behavior (Kertesz et al. 2008), and donepezil has been reported to worsen behavior in Bv-FTNCD (Mendez et al. 2007).

These observations with donepezil prompted recommendations to avoid acetylcholinesterase inhibitors in FTNCD (Arciniegas and Anderson 2013; Mendez 2009). A further potential harm of acetylcholinesterase inhibition is the risk of increasing oral secretions and contributing to aspiration in the subset of FTNCD patients who have associated motor neuron disease (Lomen-Hoerth et al. 2002).

Memantine

Excessive activation of *N*-methyl-D-aspartate (NMDA) receptors by glutamate may contribute to neuronal death in a wide variety of acute and chronic neurological disorders (Kerchner et al. 2000; Lipton 2006), including FTNCD. Memantine is a low-affinity, use-dependent uncompetitive NMDA receptor antagonist that stabilizes NMDA receptor function and glutamatergic signaling (Parsons et al. 2007). Memantine also modulates activity at nicotinic acetylcholine receptors, serotonin 5-HT_3 receptors, catecholamine transporters, and other nonselective central nervous system targets at pharmacokinetically relevant concentrations (Parsons et al. 2007).

Initial reports suggested that memantine may reduce agitation and other neuropsychiatric symptoms among persons with Bv-FTNCD (Swanberg 2007). However, in an uncontrolled study of 16 Bv-FTNCD patients (Diehl-Schmid et al. 2008), memantine had no effect on behaviors. A similarly designed study of memantine in 21 patients with Bv-FTNCD, 13 with semantic dementia, and 9 with PNFA reported transient improvements in neuropsychiatric symptoms in the Bv-FTNCD group (Boxer et al. 2009). In both studies, patients tolerated memantine well at 20 mg/day (the same recommended dosage for treatment of AD) with no significant adverse reactions (Boxer et al. 2009; Diehl-Schmid et al. 2008). A more recent open-label uncontrolled study of 16 patients with Bv-FTNCD or Lv-FTNCD treated with memantine showed an associated improvement in metabolic activity in key frontal brain regions as measured by fluorodeoxyglucose positron emission tomography but no behavioral or symptomatic benefits (Chow et al. 2011).

A 52-week randomized, double-blind, placebo-controlled phase II trial of memantine 20 mg/day for Bv-FTNCD demonstrated no effect on neuropsychiatric symptoms, cognition, disability, or caregiver burden (Vercelletto et al. 2011). Similarly, a recently completed 26-week randomized, parallel group, double-blind, placebo-controlled study of memantine 20 mg/day for Bv-FTNCD or semantic dementia observed no effects of treatment on neuropsychiatric symptoms or clinical global change (Boxer et al. 2013). Although memantine was well tolerated physically, patients treated with this medication had higher rates of adverse cognitive effects than those treated with placebo (15% versus 2%). Findings from these studies cast doubt on the hypotheses suggesting that up-regulation of NMDA receptors in persons with FTNCD presents an appropriate drug target and has engendered calls to refocus efforts on the development of disease-modifying therapies for this condition (Hodges 2013).

Emerging Treatments

Disease-modifying therapies likely will be protein-specific, growing directly out of basic science studies of FTLD-related proteinopathies involving tau, TDP, and FUS. Such therapies could potentially offer disease-modifying benefits in both AD and a subset of FTNCD syndromes,

including some cases of Bv-FTNCD and most cases of PNFA.

Davunetide reduced tau neuropathology in a mouse model (Matsuoka et al. 2008) and is being tested in a Phase II randomized, double-blind, placebo-controlled trial for patients with predicted FTLD-tau pathology. Methylene blue reduces tau aggregation and slows AD progression (Wischik and Staff 2009), and a clinical trial of a second-generation version of this compound is under way. Other potential therapies include inhibitors of enzymes that contribute to tau phosphorylation (glycogen synthase kinase-3β [GSK3β] or cyclin-dependent protein kinase 5), manipulation of tau-processing pathways (e.g., ubiquitination), and/or reduction of tau expression (Trojanowski et al. 2008; Vossel and Miller 2008). Lithium and valproic acid, inhibitors of GSK3β, are also being investigated as neuroprotective treatments for FTNCD.

FTLD-TDP neuropathology in some cases results from low levels of progranulin. Loss-of-function mutations in progranulin result in a haploinsufficiency of the protein and cause familial, autosomal-dominant frontotemporal dementia with FTLD-TDP (Baker et al. 2006). Although the exact function of progranulin is unknown, normalizing protein levels could be a potential therapeutic strategy. Recently, microRNA-29b was shown to enhance progranulin expression in vitro (Jiao et al. 2010). Other possible therapeutic strategies include reducing TDP-43 hyperphosphorylation, ubiquitination, cleavage, and translocation from nucleus to cytoplasm (Neumann et al. 2006).

As protein-specific therapies emerge, accurate in vivo diagnosis will be essential. Specifically, tools that can differentiate FTLD-tau from FTLD-TDP are needed because most future disease-modifying agents are likely to be targeted toward one pathway or the other. Neuroimaging will play a critical role in this effort (Knopman et al. 2009). A large longitudinal study is recruiting patients with FTNCD in order to longitudinally characterize their brains functionally and structurally and to develop spinal fluid biomarkers corresponding to autopsy-determined histopathologies. This study will yield not only new information on brain-behavior correlates but also strategies with which to identify the FTNCD proteinopathies in specific patients and monitoring their response to molecular treatments.

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CHAPTER 66

Vascular Neurocognitive Disorder

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Stroke and cerebrovascular disease (CVD) produce cognitive impairments and contribute to dementia due to Alzheimer's disease (AD) and other forms of dementia. The American Heart Association/American Stroke Association (AHA/ASA) defines *vascular cognitive impairment* (VCI) as "a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain" (Gorelick et al. 2011, p. 2677). AHA/ASA notes that predominant neuropathologies in older persons with "mixed dementia" are neurodegenerative changes occurring in a background of CVD (Zekry et al. 2002), including single or multiple lacunar and large-vessel strokes, ischemic leukoencephalopathy, atherosclerosis of large vessels, arteriolosclerosis, and/or microscopic hemorrhages (Middleton et al. 2011), as well as global or regional decreases in cerebral blood flow (CBF).

Vascular dementia (VaD), renamed *vascular neurocognitive disorder* in DSM-5 (see Box 66–1) (American Psychiatric Association 2013), is diagnosed with the highest specificity using the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for VaD (Román et al. 1993). These criteria have been used in most controlled clinical trials of treatments for VaD and yield three main subtypes defined by their temporal presentation profiles: acute, subacute, and chronic (Román 2010).

Box 66–1. DSM-5 Diagnostic Criteria for Major or Mild Vascular Neurocognitive Disorder

A. The criteria are met for major or mild neurocognitive disorder.

B. The clinical features are consistent with a vascular etiology, as suggested by either of the following:

1. Onset of the cognitive deficits is temporally related to one or more cerebrovascular events.
2. Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function.

C. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits.

D. The symptoms are not better explained by another brain disease or systemic disorder.

Probable vascular neurocognitive disorder is diagnosed if one of the following is present; otherwise **possible vascular neurocognitive disorder** should be diagnosed:

1. Clinical criteria are supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease (neuroimaging-supported).
2. The neurocognitive syndrome is temporally related to one or more documented cerebrovascular events.
3. Both clinical and genetic (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) evidence of cerebrovascular disease is present.

Possible vascular neurocognitive disorder is diagnosed if the clinical criteria are met but neuroimaging is not available and the temporal relationship of the neurocognitive syndrome with one or more cerebrovascular events is not established.

Coding note: For probable major vascular neurocognitive disorder, with behavioral disturbance, code **290.40 (F01.51).** For probable major vascular neurocognitive disorder, without behavioral disturbance, code **290.40 (F01.50).** For possible major vascular neurocognitive disorder, with or without behavioral disturbance, code **331.9 (G31.9).** An additional medical code for the cerebrovascular disease is not needed.

For mild vascular neurocognitive disorder, code **331.83 (G31.84).** (**Note:** Do *not* use an additional code for the vascular disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

Acute VaD is defined by new onset of dementia, days to weeks after a stroke. This condition may follow a single "strategic stroke" as a result of occlusion or rupture of a large-size vessel, a symptomatic lacunar stroke caused by ischemic small vessel disease, or recurrent strokes (multi-infarct dementia). Within this category is so-called "lacunar dementia," an acute VaD resulting from a single lacunar stroke involving the inferior genu of the internal capsule causing ipsilateral blood flow reduction to the inferomedial frontal cortex by a mechanism of diaschisis (Chukwudelunzu et al. 2001). This thalamocortical disconnection syndrome manifests with a sudden change in cognitive function, often associated with fluctuating attention, memory loss, confusion, abulia, psychomotor retardation, inattention, and other features of frontal lobe dysfunction but with mild focal findings such as hemiparesis or dysarthria.

The prototypic form of subacute VaD is subcortical ischemic vascular dementia (Román et al. 2002), a condition that progresses over a period of months with insidious onset of subcortical dementia, frontal lobe deficits, and depressive symptoms or "vascular depression" (Alexopoulos et al. 2002), along with psychomotor slowing, parkinsonian features, urinary disturbances, and pseudobulbar palsy, usually resulting from small vessel disease (Román et al. 2002). Symptoms are due to interruption by ischemic lesions of prefrontal-subcortical circuits supporting cognition, language, comportment, and motivation. The other main clinical forms of subacute VaD are Binswanger's disease (état lacunaire), cerebral autoso-

mal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and cerebral amyloid angiopathy, including those that present with leukoencephalopathy and/or vasculitis. Clinical course of these conditions is marked by fluctuations and gradual worsening over time.

The most common form of chronic VCI is mixed dementia (i.e., AD plus VaD). Patients with mixed dementia exhibit a slowly progressive disease over at least 1 year characterized by short-term memory loss, accompanied by other cognitive deficits, including problems with attention, orientation, language, multitasking, and instrumental activities of daily living. Neuropsychological testing reveals that the memory problems are worsened by inattention and loss of set secondary to executive dysfunction rather than simply to the inability to store new memories as typically seen in AD and other disruptions of the memory circuits such as in Korsakoff syndrome. The subcortical involvement of prefrontal circuits in patients with mixed dementia is usually secondary to chronic ischemia with periventricular leukoencephalopathy and lacunar strokes, as revealed by brain magnetic resonance imaging (MRI). When hippocampal atrophy is also observed, a mixed dementia diagnosis may be appropriate.

The multiplicity of pathogenetic mechanisms and variety of clinical presentations of VCI have complicated efforts to develop evidence-informed recommendations for the treatment of this condition (Román et al. 2010). Biomarkers, including positron emission tomography imaging of brain amyloid load and arterial spin labeling (ASL-MRI) to measure regional CBF, may further enhance selection of patients with VCI for controlled clinical trials. Pending development of biomarkers, treatment focuses on symptomatic management with nonpharmacological and pharmacological interventions as well as risk factor modification to reduce development of CVD and progression of VaD.

Nonpharmacological interventions, support, and education for patients and caregivers are important elements of the treatment of VaD and are modeled on those provided to persons with Alzheimer's disease. Readers are referred to Chapter 64, "Neurocognitive Disorder Due to Alzheimer's Disease," for a concise review of the principles of such treatments and are encouraged to apply them to the treatment of persons with VaD and their caregivers as well. VaD also is complicated by noncognitive neuropsychiatric symptoms that require careful management. These clinically important problems are discussed in excellent reviews of this subject presented elsewhere (Coffey and Cummings 2011; Weiner and Lipton 2012). In this chapter I focus specifically on the treatment of the cognitive manifestations of VaD and modifying risk factors for the development and progression of this condition.

Pharmacological Treatments

There are no medications specifically approved by the U.S. Food and Drug Administration (FDA) for the treatment of VCI or VaD. The multi-infarct concept led to the use of vasodilating agents, antithrombotic agents, ergot alkaloids, nootropic drugs, ginkgo biloba, xanthine derivates, and calcium antagonists, most of which produced minimal benefits (Román 2010). It also led to clinical trials of more useful treatments of VaD, includ-

ing acetylcholinesterase inhibitors, memantine, calcium channel blockers, and nootropic agents (Schwarz et al. 2012).

Acetylcholinesterase Inhibitors and Memantine

Independent of concomitant AD pathology, patients with VaD exhibit decreased levels of acetylcholine in the cerebrospinal fluid and reduced cholinergic markers such as choline acetyltransferase (ChAT) in the brain (Gottfries et al. 1994), with hippocampal ChAT deficits of up to 60% (Sakurada et al. 1990). The cholinergic nucleus of Meynert (nbM) is irrigated by penetrating arterioles susceptible to the effects of arterial hypertension (Román and Kalaria 2006). Ischemic lesions in the white matter and the basal ganglia can interrupt the cholinergic projections (Behl et al. 2007; Bocti et al. 2005), including CADASIL-induced cholinergic denervation (Mesulam et al. 2003). Acetylcholinergic mechanisms play a role in CBF modulation, and stimulation of the nbM increases cortical CBF. In light of the disruption of cerebral acetylcholinergic function in VaD and the role of acetylcholine in the modulation of CBF, the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine have been studied and used clinically to treat VaD.

Another medication used commonly in the treatment of Alzheimer's disease, memantine, has been studied as a treatment for VaD. Memantine is a moderate-affinity, voltage-dependent, uncompetitive, potent antagonist of the *N*-methyl-D-aspartate (NMDA) receptor. It inhibits and reverses the abnormal activity of protein phosphatase (PP-2A) that leads to tau hyperphosphorylation and to neurofibrillary degeneration in AD. Memantine has also been used in patients with VaD on the basis of its experimental efficacy in animal models of ischemia improving neuronal depolarization, mitochondrial dysfunction, and NMDA receptor activation from chronic glutamatergic overstimulation.

A meta-analysis of randomized 6-month controlled trials of the acetylcholinesterase inhibitors (AChEIs) and memantine in VaD (Kavirajan and Schneider 2007)—comprising 3,093 patients taking donepezil (three studies), galantamine (two studies), rivastigmine (one study), and memantine (two studies) and 2,090 patients assigned to receive placebo—observed small but significant treatment-related cognitive improvements. However, these cognitive improvements were of uncertain clinical importance. Compared with placebo, there were more dropouts and adverse events (anorexia, nausea, vomiting, diarrhea, and insomnia) with all three AChEIs but not with memantine, leading to the conclusion that widespread use of these drugs in VaD was not justified. A pharmacoeconomic analysis (Wong et al. 2009) demonstrated that each of these treatments was more effective than standard care for VaD but also more costly. The evidence for use of these agents in VaD therefore is mixed, but their prescription is common in clinical practice, and it is reasonable to present them to patients and their caregivers as a treatment option.

Calcium Channel Blockers

The calcium channel blockers used for the treatment of VaD include nimodipine, nicardipine, lacidipine, and fasudil. Nimodipine, a dihydropyridine-type antihypertensive agent, is the best studied of these medications and is a highly lipophilic agent that penetrates the blood-brain barrier (BBB) and affects CBF autoregulation (i.e., it produces vasodila-

tion). Nimodipine binds to slow L-type calcium receptors, preventing calcium influx into vascular smooth muscle cells and into ischemic neurons. A Cochrane Database review on nimodipine (López-Arrieta and Birks 2002) found no convincing evidence for the efficacy of this agent in AD, VaD, or mixed dementia. Accordingly, although these agents are sometimes prescribed for VaD, clinicians need to be mindful that the evidence base for this practice is not compelling.

Citicoline

Citicoline (CDP-choline or cytidine-5′-diphosphatecholine) is a naturally occurring endogenous nucleoside that functions as an intermediate in three major metabolic pathways (Secades 2011): synthesis of phosphatidylcholine (lecithin), one of the major cell membrane phospholipids; synthesis of acetylcholine; and oxidation to betaine, a methyl donor. Citicoline also appears to induce angiogenic factors and enhance stem cell proliferation after ischemic injury, favoring neurorecovery (Krupinski et al. 2012), and to increase levels of acetylcholine and dopamine. Citicoline components choline and cytidine are readily absorbed in the gastrointestinal tract and cross the BBB. In a rat model of chronic cerebral hypoperfusion, Lee et al. (2009) showed that citicoline protects against cognitive impairment. Citicoline also enhanced regrowth of dendritic spines in an experimental stroke model (Hurtado et al. 2007).

In a pooled analysis of clinical trials on acute ischemic stroke, citicoline was shown to improve recovery (Saver 2008) despite a negative recent stroke trial (Dávalos et al. 2012). Citicoline shows moderate improvement of memory and behavior in AD but no cognitive improvement in VaD. Overall results in a Cochrane Database review (Fioravanti and Yanagi 2005) of studies including individuals with vascular mild cognitive impairment (MCI), VaD, or senile dementia showed evidence of benefit of CDP-choline on memory and behavior, significant improvement on the Global Impression of Change scale, and good tolerability. The effect size was very large, indicating a strong drug effect (Fioravanti and Yanagi 2005). The safety and efficacy of citicoline on the cognitive manifestations of patients with acute ischemic stroke were evaluated using an open-label, randomized, parallel study of citicoline (1 g/day) for 12 months versus usual treatment in patients with first-ever ischemic stroke (Alvarez-Sabín et al. 2013). Citicoline-treated patients showed better outcome at follow-up in attention-executive functions and temporal orientation at 6 and 12 months. Moreover, patients treated with citicoline showed a trend toward better functional outcome, measured with a modified Rankin scale at 6 and 12 months (Alvarez-Sabín et al. 2013).

Collectively, these studies suggest that citicoline may be useful in the treatment of VaD. Because this product is not regulated by the FDA, discussion of risks and benefits and the need for assiduous monitoring for efficacy and safety are paramount when clinicians elect to recommend or endorse its use.

Risk Factor Modification

Modifying vascular risk factors and implementing stroke risk reduction strategies may lead to more effective prevention of dementia in the elderly (Barnes and Yaffe 2011; Román et al. 2012). Epidemiological studies confirmed the in-

creased risk of dementia associated with hypertension. In a population-based study in France, Tzourio and colleagues (Tzourio et al. 1999) found that in 4 years, untreated hypertensives multiplied by four the risk of cognitive decline. Diabetes mellitus (Ott et al. 1999; Pasquier et al. 2006), hyperlipidemia (Menezes et al. 2012), elevated plasma homocysteine (Seshadri et al. 2002), and smoking (Ott et al. 1998) also increase the risk of both VaD and AD. Therefore, primary and secondary prevention of stroke and CVD appears to be mandatory for the prevention of dementia.

Dietary reduction of sodium intake is crucial in the treatment of arterial hypertension. The Dietary Approaches to Stop Hypertension (DASH) diet (Sacks et al. 2001) is rich in magnesium, potassium, calcium, protein, and fiber and is low in saturated fat, cholesterol, and total fat, with emphasis on fruits, vegetables, and low-fat dairy foods, whole grain products, fish, poultry, and nuts. A diet rich in antioxidant phytophenols, such as those found in olive oil, red wine, and grape juice, appears to effectively inhibit endothelial adhesion molecule expression, explaining in part the protection from atherosclerosis afforded by Mediterranean diets.

Homocysteine and Cobalamin Interactions

Homocysteine (Hcy), a sulfur-containing amino acid, is an independent vascular risk factor that induces endothelial oxidation and worsens coronary artery disease, small and large vessel CVD, brain atrophy, ischemic brain lesions, impaired cognition, and dementia. In addition, Hcy induces global hypomethylation and increases hyperacetylation of histones, an epigenetic signature indicative of altered gene expression capable of controlling gene transcription affecting vulnerability of neurons to degeneration and apoptosis. Plasma elevation of Hcy may result from deficiencies of cobalamin, pyridoxine (vitamin B_6), and folate. Deficiency of either vitamin B_{12} or folate also inhibits purine and thymidylate syntheses and impairs DNA production, causing megaloblastic anemia and alterations of the synthesis of myelin and neurotransmitters such as norepinephrine and glutamate (Garcia and Zanibbi 2004).

The coenzyme form of vitamin B_{12} is cobalamin; humans are totally dependent on the vitamin B_{12} available in animal tissues to fulfill the daily requirements (2–3 μg/day). Cobalamin absorption is quite complex, and the elderly are prone to vitamin B_{12} deficiency (Andrès et al. 2004; Garcia et al. 2004). About 10%–15% have cobalamin levels ≤150 pmol/L, and 43% have elevated Hcy or methylmalonic acid. Up to 50% have atrophic gastritis (often from chronic *H. pylori* infection) with gastric achlorhydria and low pepsinogen secretion that prevent the release of cobalamin-protein complexes from the food and cause alkalinization of the small intestine with bacterial overgrowth that decreases cobalamin bioavailability. Such drugs as metformin and antiacid proton pump inhibitors or H_2 receptor antagonists inhibit cobalamin.

Neurological complications of vitamin B_{12} deficiency (Selhub et al. 2010) include cerebral white matter lesions, optic neuropathy, subacute combined degeneration of the spinal cord, and a mild form of sensory peripheral neuropathy with a typical stocking-and-glove distribution; most of the sensory symptoms are probably due to concomitant dorsal column involvement. Recently, Smith and colleagues (Smith et al. 2010) demonstrated that lowering Hcy with oral B vitamin treatment slowed down

the rate of brain atrophy in patients with MCI in comparison with placebo-treated controls. Likewise, a daily dose of 0.8 mg folic acid, 0.5 mg vitamin B_{12}, and 20 mg vitamin B_6 in 133 participants for 2 years resulted in slow cognitive and clinical decline in MCI in comparison with placebo in a comparable group (de Jager et al. 2012).

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a form of periodic breathing occurring during sleep characterized by periodic episodes of complete (apnea) or incomplete (hypopnea) upper airway occlusion. OSA exacerbates the effects of hypertension and other vascular risk factors on small vessel disease in the brain and is more common among persons with multi-infarct dementia than persons with AD or matched controls (Bader et al. 1996; Erkinjuntti et al. 1987). OSA is associated with white matter lesions (Harbison et al. 2003) and cerebral hemodynamic changes (Pizza et al. 2012). OSA produces nocturnal persistent and recurrent worsening of several important vascular risk factors, including bouts of hypertension, hypoxemia, hyperglycemia, and elevation of Hcy (Román 2013), yielding correlations between severity of OSA, degree of cognitive deficit, and extent of ischemic periventricular leukoaraioisis. OSA in elderly women increases significantly the risk of cognitive decline (Yaffe et al. 2011). Treatment of OSA with continuous positive airway pressure produces cognitive improvement (Ancoli-Israel et al. 2008; Canessa et al. 2011).

Control of OSA and lowering of Hcy by appropriate use of parenteral vitamin B_{12} and oral vitamin B_6 and folate appear to stabilize and improve cognition in elderly patients with mixed dementia. Additional controlled clinical trials would be needed to confirm this clinical observation and to advance the care of persons with VaD through modification of these risk factors.

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CHAPTER 67

Neurocognitive Disorder Due to Parkinson's Disease

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Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (AD). Although the diagnosis of PD requires the presence of characteristic and progressive motor abnormalities (i.e., bradykinesia, rigidity, and resting tremor) in the absence of dementia, cognitive disturbances also develop to some extent in almost all patients with PD over the course of the disease (Svenningsson et al. 2012). The spectrum of cognitive impairment in PD ranges from mild selective disturbances to global dementia (see Box 67–1; American Psychiatric Association 2013), and the cognitive clinical course and rate of decline in PD are variable (Barone et al. 2011). At the earliest stages of PD, cognitive deficits are evident in up to one-third of patients (Litvan et al. 2011). In nondemented patients with PD, overall cross-sectional prevalence of mild cognitive impairment (PD-MCI) is 19%–38% (Litvan et al. 2011). Age, disease duration, and PD severity are associated with presence of PD-MCI. The point prevalence of PD-dementia (PDD) is 30%–40% (Riedel et al. 2010), and the cumulative prevalence of PDD is approximately 80% (Aarsland et al. 2005; Reijnders et al. 2008). PDD overlaps clinically and neuropathologically with dementia with Lewy bodies (DLB), with the principal distinction between these conditions being onset of dementia in DLB before or shortly after parkinsonism and dementia in PDD developing approximately 8–10 years after diagnosis (which is anchored to motor symptoms).

Box 67–1. DSM-5 Diagnostic Criteria for Major or Mild Neurocognitive Disorder Due to Parkinson's Disease

A. The criteria are met for major or mild neurocognitive disorder.
B. The disturbance occurs in the setting of established Parkinson's disease.
C. There is insidious onset and gradual progression of impairment.
D. The neurocognitive disorder is not attributable to another medical condition and is not better explained by another mental disorder.

Major or mild neurocognitive disorder probably due to Parkinson's disease should be diagnosed if 1 and 2 are both met. **Major or mild neurocognitive disorder possibly due to Parkinson's disease** should be diagnosed if 1 or 2 is met:

1. There is no evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).
2. The Parkinson's disease clearly precedes the onset of the neurocognitive disorder.

Coding note: For major neurocognitive disorder probably due to Parkinson's disease, with behavioral disturbance, code first **332.0 (G20)** Parkinson's disease, followed by **294.11 (F02.81)** major neurocognitive disorder probably due to Parkinson's disease, with behavioral disturbance. For major neurocognitive disorder probably due to Parkinson's disease, without behavioral disturbance, code first **332.0 (G20)** Parkinson's disease, followed by **294.10 (F02.80)** major neurocognitive disorder probably due to Parkinson's disease, without behavioral disturbance.

For major neurocognitive disorder possibly due to Parkinson's disease, code **331.9 (G31.9)** major neurocognitive disorder possibly due to Parkinson's disease. (**Note:** Do *not* use the additional code for Parkinson's disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

For mild neurocognitive disorder due to Parkinson's disease, code **331.83 (G31.84).** (**Note:** Do *not* use the additional code for Parkinson's disease. Behavioral disturbance cannot be coded but should still be indicated in writing.)

The heterogeneous profile of cognitive impairment in PD reflects a broad range of cognitively relevant neuropathologies, including subcortical and cortical Lewy bodies; degeneration of norepinephrine-, dopamine-, and acetylcholine-containing neurons; and Alzheimer-type neurofibrillary plaques and tangles (Braak et al. 2004). The cognitive impairments arising from these neuropathologies affect functioning and quality of life even more than do the motor aspects of PD (Hely et al. 2005, 2008). In clinical practice, however, dementia is recognized in no more than one-fourth of affected PD patients (Hu et al. 2011), and detection rates for milder but still disabling cognitive impairment are even lower. Accordingly, cognitive dysfunction in PD is both underrecognized and undertreated.

Although the complex pathophysiology of PD provides multiple options for developing pharmacological and nonpharmacological treatments of cognitive deficits in PD, there have been relatively few studies on treatment of cognitive impairment in PD. Two evidence-based medicine reviews on treatment of nonmotor aspects of PD, one conducted by the Movement Disorder Society (Seppi et al. 2011) and the other by the European Federation of Neurological Societies and the Movement Disorder Society—European Section (Horstink et al. 2006), provide detailed reviews of clinical trials addressing PD-related cogni-

tive impairment. Most medication-based clinical trials focused on cognitive impairment in PD have evaluated drugs initially developed for AD (Dubois et al. 2007). Findings from these reviews support the thesis that modulation of neurotransmitter systems affected by PD has the potential to impact discrete cognitive functions (Kehagia et al. 2010).

Although clinically important neuropsychiatric disturbances co-occur at higher rates in PD patients with cognitive impairment than in those without, these disturbances are not addressed in detail in this chapter. Readers seeking information about the treatment of noncognitive neuropsychiatric disturbances in PD will find excellent reviews of this subject elsewhere (Coffey and Cummings 2011; Weiner and Lipton 2012). Instead, in this chapter we focus more specifically on the treatment of cognitive impairments among persons with PD.

Pharmacological Treatments

Dopaminergic Medications

Dopamine replacement therapy, whether via levodopa, dopamine receptor agonists, monoamine oxidase type B (MAO-B) inhibitors, or catechol O-methyltransferase (COMT) inhibitors, has the potential to treat motor dysfunction as well as improve cognition by ameliorating the aspects of executive function and working memory that are subserved by frontostriatal dopamine pathways. A first step in treatment planning for any patient, therefore, is to consider the impact of his or her motor treatment and determine whether antiparkinsonian medication adjustments could enhance cognitive function or whether these medications are aggravating cognitive dysfunction.

The effects of administering dopaminergic medications on cognition and motor function are potentially dissociable at stages during the course of PD when there are disparate extents of degeneration in the dopamine-producing neurons serving these functions (i.e., those neurons in the ventral tegmental area and substantia nigra, respectively). Dopamine-dependent cognitive functions include tasks that require cognitive flexibility, such as task switching, planning, response inhibition during periods of uncertainty, and working memory (Kehagia et al. 2010). These cognitive functions would be expected to improve in response to administration of a medication that augments cerebral dopaminergic function. By contrast, specific aspects of visual function and mental rotation and visual recognition memory are dopamine independent and would be expected either to not change or to potentially worsen in response to administration of cerebral dopamine-augmenting medications (Kehagia et al. 2010). In fact, dopamine-induced cognitive deficits are greatest on tasks that involve learning, including reversal learning and concurrent learning.

Therefore, it is not surprising that the evidence on the effects of dopaminergic medications on cognitive impairments in PD is mixed, with reports describing dopaminergic drugs improving, worsening, or having no effect on cognition in patients with PD (Cools 2006). In fact, dopaminergic medications, when prescribed in early PD, may contribute to cognitive deficits and produce impulsivity. This is particularly the case with dopamine agonists, which are linked to development of problems with impulse control and pathological gambling (Kulisevsky and Pagonabarraga 2010). For example, prami-

pexole, a dopamine D_2/D_3 agonist, can worsen cognition by causing additional difficulties related to executive function, verbal short-term memory, and verbal fluency, as well as contribute to impulsivity. Similar effects are not observed with pergolide, which acts on D_1/D_2 receptors (Kehagia et al. 2010).

Rasagiline, a second-generation, irreversible inhibitor of MAO-B (the major enzyme responsible for metabolizing dopamine in the brain), lessens the motor symptoms of PD by inhibiting the breakdown of dopamine, thus enhancing central dopaminergic transmission. In a 12-week, multicenter, double-blind study involving 48 cognitively impaired but nondemented patients with PD, rasagiline significantly improved attention (evaluated via the backward digit span test) compared with placebo. On assessments of executive function, rasagiline also significantly improved verbal fluency total scores (Hanagasi et al. 2011).

Acetylcholinergic Medications

PD is associated with a deficit in cortical levels of acetylcholine, and these deficits are profound in PDD—exceeding those observed in AD (Hilker et al. 2005). Although anticholinergic drugs (e.g., benztropine and trihexyphenidyl) are used to treat PD-related tremor, they adversely affect cognition and are best avoided in patients with PD. After anticholinergic medications are eliminated, treatment with acetylcholinesterase inhibitors may be considered. More than 20 reports describe the effects of acetylcholinesterase inhibitors (i.e., donepezil, galantamine, rivastigmine, tacrine) on cognition as well as hallucinations and dementia-related behavioral disturbances in PDD and DLB (van Laar et al. 2011). Most of the reported studies include relatively small numbers of subjects and demonstrate that individual responses to treatment are variable. On balance, however, the acetylcholinesterase inhibitors are relatively safe and appear to improve global status, cognitive dysfunction, hallucinations, behavioral disturbances, and activities of daily living among persons with PDD.

In clinical practice, all commercially available acetylcholinesterase inhibitors are prescribed. No acetylcholinesterase inhibitor is clearly superior to the others in terms of efficacy, although the data regarding the use of rivastigmine in PDD are the best developed. In fact, only rivastigmine has been studied as a treatment for PDD in a large randomized clinical trial, which supported its approval for this purpose by the U.S. Food and Drug Administration (Emre et al. 2004). The most common side effects of treatment with acetylcholinesterase inhibitors are gastrointestinal. Alternative drug delivery methods, such as transdermal administration (i.e., a patch), reduce the risk of this medication side effect. Acetylcholinesterase inhibitors have the potential to exacerbate tremor in PD. When these medications are prescribed to persons with PDD, beginning treatment at doses lower than those used in patients with AD may improve gastrointestinal and motor tolerability. Notwithstanding these considerations, the use of this class of medication follows the same considerations and practices as those used to treat persons with AD.

Two studies have investigated the efficacy of acetylcholinesterase inhibitors in patients with PD-related cognitive dysfunction but no dementia, and a third larger trial of donepezil for PD-MCI is in progress. A randomized controlled trial (RCT) of galantamine in this context failed to show any benefits on cognition, but subjects were not required to

have a minimum degree of impairment (Grace et al. 2009). In a small open-label study of donepezil for executive dysfunction in PD, global functioning improved (Linazasoro et al. 2005). These data are insufficient to recommend acetylcholinesterase inhibitors as an efficacious treatment for PD-MCI or related conditions, but suggest that further studies may yield data supporting their use for this purpose.

Uncompetitive *N*-Methyl-D-Aspartate Receptor Antagonists

Memantine is an uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist that has been studied as a treatment for motor as well as cognitive dysfunction in PD (McShane et al. 2006). Several trials in PD demonstrate that memantine is well tolerated in this population but inconsistently beneficial. In a 22-week RCT of memantine in 25 subjects with PDD, the memantine group had greater cognitive decline after the washout period (Leroi et al. 2009). A larger 24-week RCT of memantine in 72 subjects with PDD or DLB showed overall improved outcome on clinical global impression and improved speed on attentional tasks but no other cognitive benefits (Aarsland et al. 2009). The largest study included 199 subjects with PDD or DLB across 30 sites (Emre et al. 2010); in this study, memantine produced global improvements in the mild-to-moderate DLB group but not in the PDD group or the combined population. These studies collectively suggest that memantine is usually well tolerated and may improve overall functioning in some persons with PDD and DLB. When this medication is prescribed, dose initiation and titration follow the same approach as when it is used to treat AD.

Amantadine is another uncompetitive NMDA receptor antagonist that is used to treat motor symptoms in early PD, to reduce motor fluctuations in advanced PD, and to enhance cognition in PD. A retrospective survival analysis of 593 patients with PD demonstrated that treatment with amantadine was associated with higher Mini-Mental State Examination (Folstein et al. 1975) scores and a slower decline to a dementia endpoint, suggesting that it may delay development of dementia (Inzelberg et al. 2006). However, the potential for side effects of hallucinations and delirium in advanced patients renders this medication less suitable for use as a cognitive enhancer or stabilizer in this population.

Noradrenergic Medications

Degeneration of the noradrenergic locus coeruleus may contribute to the compromise of higher-order cognitive abilities, including set shifting and other tasks that require cognitive flexibility, that occurs in patients with PD (Kehagia et al. 2010). In some patients, therefore, noradrenergic augmentation may be a useful treatment approach. Consistent with this suggestion, an open-label pilot trial evaluated effects of atomoxetine (a selective norepinephrine reuptake inhibitor indicated for the treatment of attention-deficit/hyperactivity disorder [ADHD]) in 12 PD patients with executive dysfunction but no dementia (Marsh et al. 2009). Clinically significant improvement in executive function was observed in 75% of these patients, as indicated by the Frontal Systems Behavior Scale (Grace and Malloy 2001) Executive Dysfunction subscore and the Conners

Adult ADHD Rating Scale (Conners et al. 2004) Long Form Inattention/Memory subscore. In another RCT of 55 subjects with PD and depression, atomoxetine improved cognition and reduced daytime sleepiness despite an absence of improvements in mood symptoms (Weintraub et al. 2010). These observations suggest that augmenting cerebral noradrenergic function may be a useful cognition-enhancing strategy in patients with PD, especially for those whose impairments are relatively mild and/or predominantly dysexecutive.

Cognitive Rehabilitation

Cognitive rehabilitation involves a systematically applied set of medical and therapeutic services designed to improve cognitive functioning and participation in activities that may be affected by difficulties in one or more cognitive domains (Harley et al. 1992). Interventions of this type are intended to improve everyday function by reinforcing, strengthening, or restoring previously learned patterns of behavior and/or developing new patterns of cognitive activity or compensatory strategies. Restorative techniques focus on strategies to improve cognitive functioning to, or close to, the patient's premorbid level. Specifically, restorative techniques are used to improve recall of information over increasing periods of time (spaced retrieval) or using less intense cues (vanishing cues), whereas computerized drills and repeated prompting are used to improve memory and attention and recall of remote memories (reminiscence therapy). Compensatory techniques involve strategies that organize information to improve recall and learning. Other compensatory techniques include using multiple senses to improve learning and retrieval, procedural training to learn increasingly more complex behaviors, and external cues such as memory notebooks or calendars to improve recall. Programs may also teach, in person or with the aid of computerized devices and software, strategies to improve self-management, such as problem solving, time management, and compensation for impaired memory (Schutz and Trainor 2007).

Four reports have investigated cognitive rehabilitation or training programs for persons with PD: two are open-trial pilot studies (Mohlman et al. 2011; Sinforiani 2004), and two are small RCTs of cognitive rehabilitation programs targeting executive functioning, attention, and visuospatial abilities (París et al. 2011; Sammer et al. 2006). Although these studies involve relatively small numbers of persons with PD, they collectively provide evidence supportive of the potential benefits of cognitive rehabilitation in this population and its acceptability to patients with PD, and are consistent with a larger literature demonstrating the benefits of this treatment approach in other contexts.

Additional studies are needed to address barriers to implementation of cognitive rehabilitation as a treatment for PD, including the development of time-efficient treatment delivery methods. Also, ecologically valid outcome measures with which to evaluate the effects of cognitive rehabilitation on daily functioning and/or generalization to other areas of daily living are needed. If skills learned in cognitive rehabilitation carry over into everyday functioning and improve problem-solving and adaptive abilities, then such programs could create positive and long-lasting benefits for patients by improving quality of life and potentially decreasing caregiver burden.

When cognitive rehabilitation is used to assist persons with PD who are experiencing functionally limiting cognitive

impairments, personalized approaches to tailor treatment to individual strengths and deficits are recommended. Structuring time-limited treatment with specific and objectively evaluable goals and caregiver involvement also is recommended.

Emerging Treatments

The heterogeneity of cognitive dysfunction in PD has confounded its assessment, characterization, and treatment. Recent progress has led to standardization of clinical criteria for PDD and PD-MCI and better characterization of how these disturbances manifest and can be measured. As patients with PD live longer through more effective management of motor symptoms and medical complications, the impact of cognitive dysfunction on the patients and their families will continue to grow. Symptomatic treatments are currently available, and these should continue to be used. Medication management of cognitive dysfunction should be accompanied by education to the patient and family, office-based support, engagement with patient and caregiver support programs, and involvement in skill and compensatory strategy training for patients and their caregivers.

Medication development will increasingly focus on modifying underlying mechanisms that are associated with dementia and other cognitive decline, including synuclein deposition and amyloid deposition; enhancing neuroprotection; and facilitating neuroplasticity (Dunkel et al. 2012; Kansara et al. 2013). The development of risk reduction strategies and early detection approaches, including neurogenetically informed drug target development and advanced clinical neuroimaging methods, also may yield strategies that prevent cognitive decline, modify and/or arrest disease progression, and improve the lives of persons with PD and their families.

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PART XII

Personality Disorders

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The uncertainties of what version of the personality disorders would appear in DSM-5 complicated preparation of this part of *Treatments of Psychiatric Disorders* (TPD). Until December 2012, the proposed omission of four personality disorders—schizoid, paranoid, histrionic, and dependent—seemed imminent. Because the proposed changes were disapproved by many clinical and research leaders within the personality disorder (PD) community and were subsequently disapproved by the American Psychiatric Association (APA)–appointed independent research and clinical review committees, the DSM-IV system has been retained. Hence, from that point of view, the current chapters have largely become outgrowths, updates, and revisions of the material found in earlier editions of TPD.

One of the sobering lessons learned from this classification impasse is that significant criticisms can be directed at the empirical basis for our PD typology and, most significantly, can be directed at the clinical utility of many of the existing types. Here it is notable that narcissistic personality disorder (NPD) had also originally been slated for omission in DSM-5, but the objections from the psychoanalytic community and the revitalized appreciation for this type by some members of the DSM-5 Personality and Personality Disorders Work Group restored it to the system. No comparable advocacy occurred for the other four PD types proposed to be omitted.

Another interesting treatment-relevant debate within the DSM-5 proposal for change deserves note. At one point there was an effort to replace the criteria count method of diagnosis with narrative descriptions, so-called prototypes. It was expected that such prototypes would be more clinically familiar ("the way clinicians think") and would increase utilization of the five (six when NPD was restored) remaining PD diagnoses. Whatever the truth of those claims, the prototypes were heavily criticized for being nonmedical, unreliable, poorly written, and too theory-based, and for being destructive to the continued growth of research. The result was that the prototypes were dropped.

In the fourth edition of TPD, three advances that were relevant to treatments of PDs were highlighted: therapeutic approaches had been shown to improve substantially, the heritability of these disorders was found to be significant, and psychoanalytic therapy had been manualized. We predicted that these advances would initiate more research attention into their treatment. Regrettably that has not occurred. Among the reasons for the relatively weak growth of treatment-related research on most PDs are that there is an absence of strong advocates, the treatments are primarily psychotherapeutic, and the public health significance has not been documented. Neither the federal institutes and agencies nor pharmaceutical companies and organizations have made an investment.

The exception is borderline personality disorder (BPD). The chapter on BPD (see Chapter 70) has been entirely rewritten on the basis of the rapidly expanded knowledge base. In their review, John Gunderson, Igor Weinberg, and Lois Choi-Kain also note that despite considerable new knowledge about the neurobiology of BPD, this knowledge has yielded no real advances in the treatment of BPD. They argue that BPD may benefit quite substantially from supportive treatments, as Michael Stone concludes characterize treatments for Cluster A PDs. In contrast, in the chapter on Cluster C PDs (see Chapter 73), J. Christopher Perry argues for the continued advantage of therapies with cognitive learning and emotional expression as found in psychodynamic and cognitive models.

With psychoanalytic models of psychopathology having been replaced by a neurobiological model, psychiatry gives increasingly less attention to psychotherapy. A recent survey indicated that psychiatrists spend only about 28.9% of outpatient visits doing psychotherapy, down dramatically from 44.4% just 10 years ago, and that the proportion of psychiatrists providing psychotherapy in their outpatient practices declined from 19.1% to 10.8% in the same period (Mojtabai and Olfson 2008). This shift in practice is reflected in the decline in use of PD diagnoses—the domain of psychopathology where psychotherapies are the primary and sometimes only treatment modality.

In reading the chapters in this review of knowledge about treatment of the PDs, readers are encouraged to evaluate whether the clinical wisdom attached to suggestions for each PD's treatment constitutes an argument for retaining that disorder. In doing this, we would remind you that the absence of empirical studies for manualized treatment strategies doesn't mean that a disorder doesn't exist or is not treatable—only unstudied. Remember, also, that a reason why these disorders do not receive research attention is directly related to the declining role of psychotherapy within modern psychiatry.

Finally, a major development in the transition from DSM-IV to DSM-5 is the abolition of the multi-axial system. While some argued that placing PDs on Axis II assured that clinicians using the system would consider the personality dimension of each patient, others noted that placing these conditions on Axis II marginalized PDs. Sadly, the word "deferred" often appeared under Axis II in many medical records. While the impact of the abandonment of the five axes has yet to be determined, one can hope that it signals the arrival of personality disorders as conditions that merit the same clinical attention as other major diagnostic entities.

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CHAPTER 68

Paranoid, Schizotypal, and Schizoid Personality Disorders

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Individuals with paranoid, schizotypal, and schizoid personality disorders (PDs) have in common a disinclination to interact with others, often coupled with a diminished capacity for empathic understanding of other people's emotions. In contrast, persons with avoidant PD, albeit shy, usually are more empathic. Patients with these three disorders tend to be guarded, not so self-revealing, and therefore less amenable than are many of the other PDs to psychodynamic treatment approaches. The therapeutic literature on these disorders is sparse.

For simplicity's sake, each of the three disorders may be thought of as corresponding to a prototypical trait, selected for being the most characteristic feature (Livesley 2001). These traits are *suspiciousness* for paranoid PD (PPD), *eccentricity* for schizotypal PD (STPD), and *aloofness* (or "emotional detachment") for schizoid PD (SZPD). Individuals with these disorders also demonstrate typical defense mechanisms: paranoid persons tend to employ externalization, blaming others regardless of the problem. Schizoid persons are apt to show dismissiveness. Schizotypal persons often show some admixture of paranoid or schizoid traits; their typical defense mechanisms depend on the balance of those tendencies in their makeup. The empathic deficiency in schizotypal persons affects primarily their ability to read other people's minds correctly; their capacity for the *compassionate* aspect of empathy is often fairly well preserved. They can react with sadness, for example, upon learning of the troubles of someone else.

Although the three disorders represent categories of personality, in actual practice persons displaying enough traits to be diagnosed with one disorder will likely show at least a few traits compatible with the other two—or with still other

categories of personality disorder. Thus, a schizotypal person may show some paranoid traits, and a paranoid person may also show schizoid traits as well as narcissistic or antisocial traits. Therapists must therefore regard personality in dimensional terms: how much of the various categories does the person in question manifest? The actual admixture will affect both amenability to treatment and the optimal approach to treatment. Amenability will be less, for example, if a patient with (mainly) a schizotypal, schizoid, or paranoid configuration also has significant antisocial features.

For the three main personality types under discussion here, this chapter includes guidelines and suggestions for treatment, encompassing the broad areas of therapy: individual, group, and psychopharmacological.

Paranoid Personality Disorder

Paranoid personality may be encountered in nonpsychotic persons or may be an accompaniment of a psychotic condition such as schizophrenia, bipolar disorder, or delusional disorder. Suspiciousness, mistrustfulness, and frank misreading of the meanings and intentions of others dominate the clinical picture. The DSM-5 diagnostic criteria for PPD (American Psychiatric Association 2013) are presented in Box 68–1.

Box 68–1. DSM-5 Diagnostic Criteria for Paranoid Personality Disorder

301.0 (F60.0)

A. A pervasive distrust and suspiciousness of others such that their motives are interpreted as malevolent, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:
   1. Suspects, without sufficient basis, that others are exploiting, harming, or deceiving him or her.
   2. Is preoccupied with unjustified doubts about the loyalty or trustworthiness of friends or associates.
   3. Is reluctant to confide in others because of unwarranted fear that the information will be used maliciously against him or her.
   4. Reads hidden demeaning or threatening meanings into benign remarks or events.
   5. Persistently bears grudges (i.e., is unforgiving of insults, injuries, or slights).
   6. Perceives attacks on his or her character or reputation that are not apparent to others and is quick to react angrily or to counterattack.
   7. Has recurrent suspicions, without justification, regarding fidelity of spouse or sexual partner.

B. Does not occur exclusively during the course of schizophrenia, a bipolar disorder or depressive disorder with psychotic features, or another psychotic disorder and is not attributable to the physiological effects of another medical condition.

Note: If criteria are met prior to the onset of schizophrenia, add "premorbid," i.e., "paranoid personality disorder (premorbid)."

At the psychotic end of the paranoid spectrum, one confronts fixed delusions, as are seen in patients with pathological jealousy or in those with unyielding persecutory convictions. These false beliefs usually amount to defenses erected against feelings of weakness or insecurity in some important aspect of life.

When confronted about the false beliefs, the person reacts with anger, as though the confronter is attacking the fragile rampart on which the person's shaky self-esteem is resting. Paranoid persons are "experts" at creating self-fulfilling prophecies. The office employee who is convinced his coworkers are muttering depreciatory remarks about him behind his back may end up grimacing at them and refusing to engage in ordinary conversation. After putting up with this behavior long enough, the coworkers will in time shun him—"proving" that they were "against" him all along, even though initially they had no negative feelings about him at all. Another employee, who was let go because her work was really not up to company standards, may take a certain comfort in the (false) belief that she was fired because she was of the wrong skin color or religion, rather than that her work was consistently poor.

Individual Psychotherapy

Because of their mistrustfulness, paranoid persons seldom present themselves voluntarily for psychiatric help, let alone for psychotherapy, unless their paranoid tendencies are limited to a small domain within their interpersonal world. It often becomes the burden of parents, spouses, or sometimes a friend to persuade the paranoid person to undergo even a psychiatric evaluation. If hospitalization seems necessary, hazardous situations may arise. Families, fearing the reaction of the paranoid relative, sometimes resort to deception, saying, "We're taking you to the internist for a checkup," when actually they are on their way to a psychiatric emergency room. A paranoid person in this scenario will feel railroaded, even more mistrustful than before, and hardly appreciative of how the family was acting in his or her long-range best interests.

When working with patients with PPD, a clinician needs to use considerable tact (even more than may be pertinent to therapy with other personality types), because anything resembling direct confrontation would elicit swift protest and rejection, perhaps even abrupt quitting of the therapy. A better strategy is to enter the world of the patient as best one can—not by mindlessly agreeing with the patient's distorted assumptions, but by accepting the possibility that there could well be some truth to what the patient is asserting. Careful inquiry is then in order, in the hope that the therapist may come to discern what needles of truth may lie hidden in the haystack of the patient's misperceptions. The task is more difficult when workplace situations are involved, because clinicians rarely have access to information from collaterals, such as the patient's coworkers or superiors. When family or friends are the focus, sometimes a patient may grant permission for a clinician to interview those persons, who may contribute to a more objective view of the patient's behaviors and attitudes. The following example serves as an illustration of "entering the world" of the paranoid patient:

> A young attorney at a law firm complained to a therapist that the other employees and associates seemed to have it in for him; he said they're against him and are trying to thwart his advancement. The therapist, accepting that such a situation could really be taking place, asks the patient what he thinks their motives might be. The therapist could slip in a compliment in the phrasing of the question: "Since you're such a serious person—conscientious, prompt, and thorough—is it possible that the others—who seem so lazy and slipshod—are a bit envious of your better work habits?" A "yes" answer may lead to the attorney's adding that the others all have lunch together and never invite

him to join. The therapist could then add, "Ah well, shirkers probably don't feel comfortable around the guy who gets everything done ahead of time." The therapist's "positive spin" may help the patient feel he has an ally with whom he can begin to share his more troublesome thoughts.

The patient may now acknowledge, for example, that he wouldn't be at ease if he went with the others for a drink after work and for a chance to meet some women at the bar. He might say he doesn't have the "common touch," doesn't know how to "chat up" the women he might meet, or can't even make jokes along with the guys, and would therefore be a flop at such gatherings. Persons with PPD seldom have a robust sense of humor and don't easily admit, let alone laugh at, their shortcomings.

Paranoid persons, given what is to them an ambiguous social encounter, will assume hostility more readily than friendliness. If the person guesses wrong that a potential friend is really hostile, the price—in embarrassment and hurt—is too high. Because paranoid persons are often poor at empathic "mind reading," they cannot rely on their judgment in the social arena. This leaves them in the situation of the soldier in the jungle who must "shoot first and then ask questions."

Because the capacities for empathy and self-reflection are often meager in patients with PPD, the therapist's task in helping them gain insight and in making salutary changes in their interactions with others will be arduous, long, and only occasionally crowned with success. Treating patients with PPD is not for the impatient optimist. What is needed, besides patience, is flexibility of approach. Supportive therapy will usually be more appropriate than a psychoanalytically oriented approach. Understanding the patient's dynamics will be useful, however, in fashioning a more sympathetic and acceptable supportive therapy.

Meissner (1996) has drawn attention to countertransference reactions that paranoid patients may evoke in their therapists. Because of their tendency to be argumentative and slow to see the other person's point of view, these patients may provoke frustration and irritability in their therapists—along with a feeling of impotence and despair. Such feelings, however, serve as important clues about what the patient may be struggling with but unable to verbalize. The patient may feel impotent and despairing but too embarrassed to acknowledge this. Through the mechanism of projection, these unpleasant feelings will get externalized, foisted literally onto the shoulders of the therapist. Provided that the patient is not grossly delusional and that some working alliance has been formed, the therapist, in becoming cognizant of these feelings, may then suggest that the patient may also be saddled with these same feelings. The therapist might say, for example, "You know, the helplessness and uselessness I feel when you upbraid me as a 'tenth-rate loser of a therapist'? I get to wonder if anyone has ever put you down and made you feel worthless in that way? That could be important for us to look at."

Although not all paranoid persons are jealous, most seriously jealous persons have a pronounced paranoid streak—especially when the jealousy takes on near-delusional or frankly delusional proportions (White and Mullen 1989). Freud (1911/1958) expressed the view a century ago in regard to the famous case of the judge Daniel Schreber that delusional jealousy stemmed from repressed homosexual impulses, via projection (as if a man were to say, "I don't love him, he loves me"). In light of contemporary research, Freud's hypothesis appears to be pertinent in only a small fraction of such cases. A therapist may encounter, in-

stead, a whole variety of other underlying dynamics, such as feelings of persecution because of one's minority status, a man's fears that his child may have been fathered by someone else, and so on.

Another problem peculiar to working with paranoid persons is litigiousness. It is one of their characteristics to feel slighted when no offense was meant, or to feel they must take legal action when something goes "wrong" in their interactions with others. Those "others" may, of course, include the therapist. No therapy can flourish, of course, if the threat of lawsuit hovers constantly over the therapeutic relationship. A minor side effect of a prescribed drug may be taken personally by a paranoid patient, who experiences the prescription as an attack that the therapist "meant" to inflict upon his or her person. This points to a narcissistic element in paranoid personality: the world seemingly contains only the Self—as an island surrounded by Enemies, poised to harm or take advantage of the paranoid person's Self. I had occasion to work once with a paranoid man who, one might say, came by his mistrust of others honestly: he was sodomized by his father during his early adolescence. Once, while reading the newspaper on the subway, a young woman politely asked him if she might read the section he had finished reading. He glowered at her and said nothing. As she got off at the next stop, she muttered something unkind under her breath. I asked him whether he might have avoided that unpleasantness by saying, "I'm so sorry, but I really need both sections for my work this morning, or I'd have been glad to offer it to you." He replied, "The bitch didn't deserve it!" I could not get him to understand that he *made* her into a "bitch"—which was not likely her customary persona—by his hostile assumption and behavior (another "self-fulfilling prophecy"). In a similar vein, litigious persons create enemies, whom they then feel compelled to sue, by way of getting even. The man who had been molested by his father had such a seriously damaged self-image that he felt that people in general were hateful and regarded him as no better than an insect. He even spoke of himself at times as a "roach" who deserved nothing good in life, and he denied himself many pleasures. He told me that he had once bought a ticket to his favorite opera but then he refused to go because he was so "unworthy." I hastily handed him a prescription on which I wrote, "GO to the damn opera and enjoy it!" This was a turning point in our work. It was still hard for him to trust people, but he was afterwards able to feel entitled to indulge in the harmless pleasurable pursuits he had hitherto avoided.

Psychotherapy with paranoid patients goes more smoothly when the proportion of their life space that is affected by suspicion and mistrust is circumscribed and small. An engineer I once treated worked for a large company; he felt that his peers were prejudiced against him because he was Jewish and hence chose not to invite him to certain company gatherings. Also, others he felt were less capable than he were promoted over him. He came to the United States as a child from an eastern European country where his father, having escaped the Nazis, was being persecuted by the Communists. His life in general went well; he was married with several children and was reasonably well off. But it took little for him to imagine he was the object of prejudice. It was hard for him to accept the notion that his coworkers may simply have preferred to mingle among themselves, out of long acquaintance and shared interests, without their necessarily also harboring anti-Semitic feelings. Because it was impossible to know the truth of their sentiments,

I suggested to him that he use his skills and administrative abilities to create a firm of his own, where he would be the boss. He did this, and thus extricated himself from the portion of his life where his paranoid worries were active. His worries did not evaporate, but they were now abstract and distant.

Cognitive-Behavioral Therapy

Useful guidelines for working in the cognitive-behavioral mode with paranoid patients have been outlined by Beck et al. (1990). In cognitive-behavioral therapy (CBT), the focus is on the patient's distorted assumptions. Attention is not focused on unconscious conflicts as emphasized in analytically oriented psychotherapy. The traits of other personality disorders—such as narcissistic, obsessive-compulsive, or antisocial—can accompany PPD, but these will take second place in therapy to the paranoid preoccupations with fear of being harmed by others, and with the countermeasures of hypervigilance and reluctance to reveal much about one's inner life. The more the therapist can help the patient cope with the key life situations that trigger this defensiveness, the more the patient may be able to overcome guardedness and to greet those situations with less fear. Slowly, the exaggerated assumptions ("People don't like me"; "People are out to take advantage"; etc.) may give way to more realistic appraisal of the social field. In CBT, the ability of the therapist to start out by entering the patient's world will be a key intervention. After one patient had, for example, mentioned how he always expected the worst of people, the therapist sympathized, saying, "After all, how are you to know if it's safe to trust me or not? People tell me I have an honest face, but what does that prove? It's hard to get help without trusting at least a little, but it's hard to tell if it's safe to trust. How does that sound so far?" The patient replied, "You've got it about right."

By showing honesty and humility in interventions of this sort, a therapist can help convince a paranoid patient of the therapist's trustworthiness. The patient might then begin to think, "Here is someone who knows there is no trust-at-first-sight and is not out to con me; we see the world the same way." Little by little, reason may supplant the paranoid assumptions, and then lead to the formation of new and more adaptive habits of thought.

Group Therapy

Because of their hypersensitivity, poor empathic skills, and tendency to misinterpret the motivations and attitudes of others, paranoid patients are usually uncomfortable in group therapy. They fear mass attack, but also their responses sometimes alienate others in the group, creating (in yet another form of self-fulfilling prophecy) a situation where the others really do turn against them. In one such group, ostensibly "analytically oriented," a paranoid man told the others how he and his wife, after she had a miscarriage, proudly placed the fetus in a formaldehyde jar upon the mantle over their living room fireplace. The others lost no time in expressing how tasteless and repugnant they found this. The patient could not grasp why the others reacted as they did. Far from being able to laugh at himself for this socially offensive act, he simply felt the group was making fun of him. He abruptly quit the group. It is touchiness of this sort that poses such great obstacles in trying to carry out group therapy with paranoid patients.

In forensic hospitals, group therapy for paranoid patients is considered a use-

ful adjunct, insofar as many men (and a few women) who have committed acts of violence arising out of uncontrolled anger are placed in group therapy settings geared toward anger management. Follow-up studies are unfortunately rarely available to assess how well the group sessions may have led to better control after the patients have been released and resumed extramural life.

Pharmacotherapy

For paranoid patients, psychoactive medications have little efficacy and therefore little role in therapy. Antipsychotic medications in small doses (risperidone 1–2 mg/day; haloperidol 5 mg/day) may allay anxiety in some paranoid patients; however, the need of these patients to be always on the alert, anticipating where danger may lurk, makes them generally reluctant to take such medications (or, indeed, any medication). In forensic settings, however, medication over objection may be ordered by the court to help deal with combative or delusional symptoms. For example, a markedly paranoid man was remanded to a forensic hospital after having sliced, with a box cutter, the throat of a woman behind him in the checkout line of a grocery store. He talked to no one and refused medication, regarding it as poison. Faced with the court order, he accepted risperidone tablets. Three days later he was cheerful, conversant, and no longer in the grips of paranoid ideas. It was a mystery to him why he had targeted that woman.

In treating patients with nonpsychotic forms of paranoid personality (entrenched racial or religious bigotry, pathological jealousy, litigious "injustice collectors"), one would neither expect nor find therapeutic effectiveness via medications. Still, a few positive results have been published in noncontrolled trials of paranoid patients taking pimozide (Collard 1979; Ungvari and Hollokoi 1993).

Schizotypal Personality Disorder

STPD had been considered for the most part an attenuated form of schizophrenia, as though some of the same genes that contributed to the risk for the "parent" (and psychotic-level) illness were present also in the milder, not psychotic form of "schizotypy" (the umbrella-term for related conditions) (Kendler and Walsh 1995; Mednick and Schulsinger 1968). The DSM-5 diagnostic criteria for STPD are presented in Box 68–2.

Box 68–2. DSM-5 Diagnostic Criteria for Schizotypal Personality Disorder

301.22 (F21)

A. A pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Ideas of reference (excluding delusions of reference).
2. Odd beliefs or magical thinking that influences behavior and is inconsistent with subcultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, or "sixth sense"; in children and adolescents, bizarre fantasies or preoccupations).
3. Unusual perceptual experiences, including bodily illusions.
4. Odd thinking and speech (e.g., vague, circumstantial, metaphorical, overelaborate, or stereotyped).

5. Suspiciousness or paranoid ideation.
6. Inappropriate or constricted affect.
7. Behavior or appearance that is odd, eccentric, or peculiar.
8. Lack of close friends or confidants other than first-degree relatives.
9. Excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self.

B. Does not occur exclusively during the course of schizophrenia, a bipolar disorder or depressive disorder with psychotic features, another psychotic disorder, or autism spectrum disorder.

Note: If criteria are met prior to the onset of schizophrenia, add "premorbid," e.g., "schizotypal personality disorder (premorbid)."

Even if eccentricity (or "oddity") is accepted as the defining feature of STPD, one still must confront the blurriness of the conceptual boundaries of the disorder. Most of the traits listed in DSM-5 Criterion A do revolve around *oddity* (oddity of thought, speech, behavior, and affect); however, one of the traits is suspiciousness or paranoid ideation, which creates an inevitable overlap with the related PPD. Many schizotypal patients also show certain narcissistic traits—not so much the arrogance or entitlement of narcissistic PD proper, but rather a self-centeredness and diminished empathy for the feelings of others.

Clinical Considerations

The remarks in the preceding paragraph serve to highlight the diversity of clinical presentation among persons meeting criteria for STPD. The following brief vignettes illustrate some of this diversity. It is important to note at the outset, however, that thus far there have been no randomized controlled studies or evidence-based treatments devoted to STPD. This is not surprising. In patients within the domain of PDs, studies of this sort are best carried out when the changes to be measured are based on behaviors that are 1) easier to document and 2) more amenable to change via treatment. Such change is less easily effected in patients with STPD and SZPD.

The persons in the case vignettes that follow had been in treatment for STPD; eccentricity was a major attribute of each. Two of the patients had mothers who had been hospitalized repeatedly for schizophrenia. For all three patients, *supportive psychotherapy* seemed the most pertinent and useful therapy.

Case 1—Main Traits: Odd Speech, Odd Thoughts

The patient was a woman in her 20s whose speech was filled with elusive poetical references and strange metaphors, all expressed in a highly circumstantial manner that made her difficult to understand. She had strange religious preoccupations, which she preferred to dwell on during her sessions rather than discuss the problems in her personal life. However, her affective empathy was quite intact. She had one close friend with whom she eventually shared her life. She was able to sustain herself through her work, which involved little interaction with others. Supportive therapy was helpful in that the patient was encouraged to speak more directly about the problems in her relations with others, and was eventually more able to do so, without relying so much on a private language to avoid talking about what really mattered.

Case 2—Main Traits: Odd Thoughts, Odd Behavior

The patient was a woman in her 40s, independently wealthy but lonely

and reclusive, who tried to guide her life by astrological signs. She once warned me that "trouble was coming" because "the full moon was now in Aquarius's house." She had only one friend, an astrologist who assured the patient that knowing one's moment of birth, down to the minute if possible, would allow the astrologist to give an accurate forecast of how a person's life would unfold. Through supportive therapy, the patient was encouraged to broaden her social life by setting up scholarships where she got to choose and get to know the students she helped to support.

Case 3—Main Traits: Magical Thinking, Paranoid Ideas

The patient was a man in his late 20s whose main schizotypal traits were ideas of reference and suspiciousness. His affect was also inappropriate, consisting of a fixed smile unrelated to what was happening in his immediate surround. He was grandiose, imagining that he could one day assume the reins of one of the large companies headed by his parents' friends—despite his having no relevant training or experience. He would also attribute hidden meanings to the first letter of a newspaper article that caught his attention—as though it referred somehow to him. He also attached significance to meaningless differences in such matters as the size of the letters of a signature on a postcard from a family friend: he commented that the R of the man's signature was smaller than the R on his previous correspondence, which the patient construed as representing his having fallen out of favor with that man. This patient demonstrated a generous admixture of paranoid traits alongside the schizotypal ones. Supportive therapy with this man consisted of encouraging him to work on his painting and photography, areas in which he had talent. His efforts in these areas allowed him eventually to take pride in his accomplishments and to see himself as a more substantial person.

Drug Abuse as an Aggravating Factor

Among the mind-altering drugs that can provoke a schizotypal reaction or aggravate a preexisting STPD, cannabis takes pride of place. The drug problem appears worse than in previous generations, because the use of cannabis has become almost a rite of passage into adolescence, and the tetrahydrocannabinol (THC) content in marijuana is often stronger than it once was (Kleber and DuPont 2012). As Anglin et al. (2012) mention, cannabis use prior to age 14 is a strong predictor of schizotypal symptoms in adulthood.

Clinicians dealing with young patients presenting with STPD should inquire carefully about the use of cannabis and other mind-altering drugs. If these substances appear to play a significant role in the personality pathology, the clinician should strongly encourage such patients to refrain from using them. Enrollment in a drug treatment facility may become a crucial first step in curbing the abuse problem, which (if successful) may help reduce the schizotypal manifestations.

Individual Psychotherapy

The types of individual psychotherapy currently used in the treatment of schizotypal patients can be classified under three headings: 1) *dynamic,* 2) *cognitive-behavioral,* and 3) *supportive.* These therapies and their variants have been well described in books by Gunderson (1984, 2001), whose focus was on patients with borderline personality disorder (BPD). Dynamic and cognitive-behavioral therapies are, in my clinical experience, sometimes applicable to schizotypal patients, but with the proviso that, compared with BPD patients, fewer schizotypal patients

will reap significant benefits from analytically oriented or strictly behavioral interventions. In the domain of STPD, absent the kind of controlled studies of psychotherapy with research designs that might, if feasible, have placed treatment recommendations on a more secure footing, the therapist must rely on the accumulated wisdom of clinicians who have worked with schizotypal patients in large enough numbers and over long periods of time.

Dynamic Psychotherapy

Dynamic therapies include psychoanalytically oriented or psychoanalytically informed modalities such as intensive-exploratory (Gunderson 1984, pp. 52 ff.) and transference-focused (Clarkin et al. 1999) psychotherapies. Dynamic therapies for STPD rely on the presence of high patient motivation for treatment, good psychological mindedness (or reflective capacity), ability to work with symbolism and dreams, and sufficient stability so as not to have the work interrupted too often by storms of intense negative affect. Reflective capacity involves adequate empathic ability: being able to grasp the other person's emotional and mental state, as well as to recognize and think about one's own inner conflicts (Bateman and Fonagy 2004, p. 75). Not many schizotypal patients with concomitant paranoid traits come well equipped with this capacity; this limits the proportion of schizotypal patients who are readily amenable to the dynamic therapies. For those who are, twice-weekly sessions are indicated, because transference aspects are less apt to become recognizable on a less frequent schedule. Openness to new ideas and new ways of thinking about oneself and others is an important aspect of amenability to dynamic therapy (Widiger et al. 2002). Schizotypal persons often show a good measure of openness, apart from those who, as mentioned, have strong paranoid features. Gabbard (2005) considers classical psychoanalysis (use of the couch for three or four sessions a week) as contraindicated for schizotypal patients, largely because of their fragility (and proximity to schizophrenia).

Cognitive-Behavioral Therapy

Almost all schizotypal patients show deficits and peculiarities in social behavior, for which Beck et al. (1990) offer specific remedies. One of the explicit goals in Beck's approach is to make the schizotypal patient more keenly aware of his or her *automatic thoughts and assumptions,* focusing on those that exert a deleterious influence on the patient's life (Beck and Freeman 1990, p. 139). Therapists with a psychoanalytic background might prefer picturing these as unconscious or repressed ideas that nevertheless steer the patient helplessly along maladaptive channels. Among the automatic thoughts described by schizotypal patients, Beck lists, "I have a feeling something bad is going to happen," "I know they are not going to like me," "I can feel the devil in her," and "I am a non-being" (Beck and Freeman 1990, p. 139). Other automatic thoughts of schizotypal patients relate to magical or clairvoyant thinking: "I can predict the future" or "I have a sixth sense."

Supportive Psychotherapy

Supportive measures are more widely used with schizotypal patients than are dynamic techniques. The specific measures, such as encouragement, fostering adaptive skills, and the like, have been outlined by Winston et al. (2001).

Appelbaum (2005) adds to the list additional measures such as responding directly to a patient's questions (generally avoided in dynamic therapies) and

avoiding confrontation and interpretation (at least in the early stages of therapy). Elsewhere, I mentioned that in working with schizotypal patients, the therapist often serves as an "auxiliary ego" (Stone 1993, p. 187). I offered the following example:

> A schizotypal woman met a man at a picnic, who called her the next day for a date. He was calling from a pay phone but told her it had no number on it, adding that he had no landline because his apartment lease was about to expire. She asked me, "Should I accept a date with him or not?" emphasizing how lonely she was and how tempted to accept a date. I told her she must have worries, or she wouldn't have asked me. She replied that he told her "I want 100% honesty!" and asked me if that perhaps meant he wasn't being 100% honest with her. I then asked her, "If you were in the Maine woods, and I wasn't around, what would your instincts tell you?" She said, "I think he's shifty." Through supportive measures, in other words, I helped her to make the proper inferences (to "connect the dots," as we say) that in her loneliness she had suppressed. She then realized what was only half-conscious before: that the man was most unpromising as a "date" prospect.

Sometimes therapists in their role of auxiliary ego find it necessary to teach a schizotypal patient a lesson in everyday manners. The woman in the previous vignette, for example, used to leave an apple core on the table of my waiting room before her sessions. After I asked her not to do that, she came to her next session and left a banana peel on the table. Unable to generalize from what others would understand as an all-inclusive injunction, she said (when requested not to leave *any* half-eaten food on the table), "You didn't say anything about bananas."

Need for Flexibility in Psychotherapy

In working with schizotypal patients for any length of time, therapists will face emergency situations, such as suicidal impulses or gestures, which call for supportive measures (limit setting, hospitalization, etc.); instances of phobic avoidance or of ignorance about the ways of the world or of a need for validation, which call for CBT; and stretches of time when things are calmer, when dynamic measures can be useful. No one-size-fits-all approach is universally applicable to schizotypal patients; the therapist needs to be flexible about use of the various techniques. Some authors have called this an "integrated" approach (e.g., Judd and McGlashan 2003; Livesley 2012). The following vignette, about a woman with (primarily) schizotypal but also borderline and histrionic traits, as well as obsessive-compulsive disorder, illustrates this need. In this case, the eclectic approach relied mostly on psychoeducative and behavioral interventions.

> A 30-year-old single woman sought continuing therapy after a hospitalization for a suicide gesture. She was overly sensitive emotionally, although her empathic capacity was intact. Her mind was dominated by magical thinking, superstitiousness, and odd beliefs, many of which concerned cleanliness and sex. She developed anorexia nervosa during adolescence; her tendency to self-starve persisted. Her identity disturbance was pronounced: she saw herself as "fat," despite never weighing more than 100 pounds and sometimes dipping dangerously into the low 80s. If she walked past a fat woman in the street, she worried that she would become pregnant. When in the car next to her boyfriend, she worried that his sperm would somehow jump out onto the steering wheel and then to her skirt

and get inside to make her pregnant. There was a need for sex education in this otherwise bright, college-educated woman. She was phobic about germs and sent all her clothes and bedding to the cleaners every day. She couldn't touch money. This last issue was resolved by a behavioral maneuver: I dropped dollar bills onto her hands during her sessions, by way of reassuring her that she would "live to see another day." The color black meant "death" to her (specifically, the death of her father), and she asked that books with a black cover be turned around. I encouraged her to endure the sight of the black books, come what may; after a time, this no longer bothered her. Additional behavioral measures were used to desensitize her to other fear-inspiring situations. In the early stages of therapy, she had brief dissociative experiences whenever, during a session, the topic turned to sex or to her mother. She would stare into space, be momentarily "in a different world," and then whisper, as though her mother, who lived far away, could overhear what she said. After some 5 years of thrice-weekly therapy, the woman met a suitable man, married him, and later had a child. Albeit still overly sensitive and quite thin, she has by now largely recovered.

Group Therapy

For many schizotypal patients, group therapy may play an important role, usually as an adjunct measure alongside the patient's individual therapy. Fearfulness and mistrust of others may in some instances interfere with a patient's willingness to participate in group therapy. Piper and Ogrodniczuk (2005) cautioned that schizotypal patients who are particularly eccentric or odd appearing may pose a challenge for the more conventional patients in the group. These authors spoke of another potential impediment: some schizotypal patients are inordinately shy and uncomfortable speaking up in a group—an inhibition that ongoing individual therapy may help the patient to overcome. Under ideal circumstances, the group can serve as an excellent crucible for melting down the patient's negative assumptions (of the sort outlined by Beck et al. [1990]), such as "People won't like me" or "My fantasies are too weird and embarrassing." If these obstacles can be overcome, the patient may be able to form a more realistic self-image.There are many varieties of group therapy; those suitable for schizotypal patients should have a leader who is directive, engaging, and sympathetic, unlike in certain analytically oriented groups in which the leader purposely sits in silence for a long time, waiting to see what emerges spontaneously from the group members without offering cues or suggestions.

Family Therapy

Young schizotypal patients are often caught in intense family situations similar to those arising in the families of certain patients with schizophrenia. Schizotypal patients are more likely than people in the general population to have a parent or sibling with a schizophrenia spectrum disorder. Indeed, the family may contain several persons who are psychologically fragile or hard to reason with. Even if the parents are functioning well, however, they may misunderstand the nature and chronicity of the patient's condition and, lacking this awareness, may entertain unrealistic expectations about what their son or daughter may achieve. When a patient is particularly bright, it is often hard for parents to grasp that high intelligence may not offset the social and occupational disadvantages that the schizotypal condition imposes on their child. In this situation, family

therapy will be oriented in part to educating the parents about the discrepancy between their hopes and reality. This may help to reduce the family's impatience or negativity toward the schizotypal child (Anderson 1989).

In some families in which there is a schizotypal young person, there may be a turbulent or hostile atmosphere; in these cases, psychoeducation is not the first order of the day. The therapist needs to deal first with the more immediate problem of lowering the tension in the family, such as by getting the parents to stop criticizing or humiliating the schizotypal child as just being "lazy" or "weird" or "disrespectful." For example, a schizotypal young person may have dropped out of college and been unable to sustain any employment, and one or both parents have been verbally abusing the child as being a "hopeless lay-about" undeserving of further financial (or psychotherapeutic) help. The family therapist in such a situation needs to calm the family's anger and deal with their disappointment as a first order of business, before they can then be educated about the nature and prognosis of their child's schizotypal personality.

Pharmacotherapy

Schizotypal patients exhibit traits that span a wide range, from the standpoint of symptom and personality categories, all the way from persons in close proximity to having unequivocal schizophrenia (with strange ideas that approximate actual delusions) to those with just eccentric views, odd thoughts, and perhaps some paranoid tendencies. Some schizotypal patients never have psychotic "breakdowns," however brief, whereas others require occasional (though generally not very prolonged) hospitalizations. In general, schizotypal patients show fewer of the flamboyant symptoms (suicide acts and threats, self-mutilation, rage outbursts) that are common in patients with BPD. The various attributes of STPD make for less clear-cut end points in measuring success with pharmacological interventions. This may account for the relative dearth of randomized controlled trials involving schizotypal patients, compared with the greater number dedicated to patients with BPD.

Given the diversity of clinical presentation among schizotypal patients, there can be no unitary prescription for optimal pharmacology for STPD as a clinical entity. Patients with STPD nearer the schizophrenic pole tend to benefit from antipsychotic medications—often in small doses, and for relatively brief periods. In an early random-sample 3-month study of patients with STPD and BPD, those with cognitive disturbance and ideas of reference showed improvement with neuroleptics (thiothixene proving better than haloperidol), whereas those with prominent anxiety benefited from anxiolytics (Serban and Siegel 1984). In a meta-analysis of pharmacotherapy for severe PDs (including STPD and BPD), antipsychotic medications were noted to have a moderate positive effect on cognitive-perceptual symptoms; for global functioning, mood stabilizers proved useful but antidepressants hardly at all (Ingenhoven et al. 2010). In another study, 25 patients with STPD were treated in randomized fashion with low-dose risperidone (14 given the active drug; 9 given placebo); five patients had comorbid BPD (Koenigsberg et al. 2003). Improvement was noted within 3 weeks for negative symptoms (via the Positive and Negative Syndrome Scale) and within 7 weeks for positive symptoms. When prominent paranoid traits are present in STPD, medication is not typically useful; the patient may even worry about ingest-

ing "harmful foreign chemicals" or balk at taking a substance that may interfere with the vigilance that paranoid persons are loathe to sacrifice. By the same token, STPD patients with prominent paranoid traits are less likely to participate in controlled studies, so less is known about their responses to various treatments from research findings than from the less rigorous source of clinical experience.

Schizoid Personality Disorder

Schizoid personality, with its main trait of aloofness, is less closely connected with the schizophrenia spectrum than is schizotypal personality. Factors other than genetic risk may also lead to this personality configuration. The DSM-5 criteria for SZPD are presented in Box 68–3.

Thanks to the aloofness by which SZPD is often identified, persons with SZPD seldom voluntarily seek psychiatric treatment, just as they eschew contact with people in general. Those who do show up for psychiatric help do so reluctantly, and have usually been prodded by family members in reaction to some peculiarity that has created problems for the other family members. Schizoid persons tend to have few if any friends, make little or no eye contact, and are loathe to volunteer information about themselves. As an example, a teacher in her late 20s was urged by her relatives to seek therapy. I worked with her for about a year, during which time she looked only at the floor, did not speak spontaneously but only in response to my questions, and appeared to feel deeply ashamed about something. She did acknowledge feeling like a "bug." Eventually she quit therapy. I never developed any clear idea about her psychodynamics, although I was aware that no relatives had psychiatric disorders (let alone schizophrenia). She was an only child whose father had died when she was age 3 years, so there were no "skeletons in her closet" such as incest to account for her extreme reticence. Years later I learned, by coincidence and from a mutual acquaintance, that this woman was homosexual. My contact with her was in the late 1960s, at a time when social opprobrium about being gay was much stronger than it is today. I believe this accounted for her self-imposed isolation and introversion, which combined to yield a schizoid picture, based primarily on environmental rather than hereditary factors. A trial of anxiolytic medication did not yield any benefit—as is routinely the case when treating schizoid patients. Whereas self-loathing was a key factor in this teacher, other schizoid persons have introversion that stems primarily from genetic predisposition. These individuals may be amenable to group therapy, where acceptance and sympathy by the group members can eventually help them overcome their reluctance to interact with other people.

Box 68–3. DSM-5 Diagnostic Criteria for Schizoid Personality Disorder

301.20 (F60.1)

A. A pervasive pattern of detachment from social relationships and a restricted range of expression of emotions in interpersonal settings, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

1. Neither desires nor enjoys close relationships, including being part of a family.
2. Almost always chooses solitary activities.

3. Has little, if any, interest in having sexual experiences with another person.
4. Takes pleasure in few, if any, activities.
5. Lacks close friends or confidants other than first-degree relatives.
6. Appears indifferent to the praise or criticism of others.
7. Shows emotional coldness, detachment, or flattened affectivity.

B. Does not occur exclusively during the course of schizophrenia, a bipolar disorder or depressive disorder with psychotic features, another psychotic disorder, or autism spectrum disorder and is not attributable to the physiological effects of another medical condition.

Note: If criteria are met prior to the onset of schizophrenia, add "premorbid," i.e., "schizoid personality disorder (premorbid)."

Many schizoid persons in the community function well in their occupation (often of a scientific or academic nature) and never feel the need for psychiatric intervention. Those whose symptoms lead them or their family members to seek psychiatric help are often struggling (like the teacher in the example) with feelings of shame. Supportive psychotherapy is the main treatment modality. Schizoid patients tend not to interact much in group therapy settings, so group therapy is seldom useful. The same is true of family therapy, apart from working with just the relatives to make them acquainted with the patient's problems and social handicaps. Psychopharmacological interventions are not useful in "pure" SZPD, although it may be helpful if other traits (e.g., schizotypal traits) or symptoms (e.g., anxiety or depression) are also present.

Conclusion

The treatment of any of the three personality disorders discussed in this chapter—schizotypal, paranoid, or schizoid PD—is challenging. Schizotypal patients are probably the most amenable to therapy because they are usually more prone to form relationships (including with a therapist) and to seek help than are patients with the other two types. Paranoid patients rely chiefly on the defense mechanism of externalization (i.e., blaming others instead of acknowledging internal conflicts), and thus require deft handling in which the therapist initially accepts rather than challenges their exaggerated assumptions. Schizoid patients, because of their aloofness and avoidance of human contact, need to be encouraged to increase their repertoire of solitary pleasures. Supportive psychotherapy will form the main treatment approach for each of the three types, but each will require a somewhat different selection from the overall menu of supportive interventions.

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CHAPTER 69

Antisocial Personality Disorder

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Antisocial personality disorder (ASPD) is the most reliably diagnosed condition among the personality disorders, yet treatment efforts are notoriously difficult. Many psychiatrists are reluctant to treat patients with ASPD because of widespread belief that such patients are always untreatable. There is increasing evidence, however, that ASPD may, in certain cases, be treatable.

In this chapter, we briefly review historical and contemporary nosological controversies regarding the ASPD construct, and summarize the general research findings for this condition. We then discuss treatment planning in detail, based on thorough assessment of the individual's personality characteristics to determine prognosis, risk management, and appropriate treatment. We conclude by evaluating the specific treatment approaches available for ASPD, drawing from our own clinical experience and the research evidence to date.

Psychodiagnostic Refinements

Before any treatment efforts are undertaken, diagnostic refinement is critical, especially determination of the degree of psychopathy, in the patient diagnosed with ASPD. The older, clinical tradition for understanding ASPD used the term *psychopathy* or *psychopathic personality* and was most thoughtfully delineated by Cleckley (1941/1976). This tradition is distinguished by attending to both manifest antisocial behavior and personality traits; the latter are described as the callous and remorseless disregard for the rights and feelings of others (Hare 1991) or aggressive narcissism (Meloy 1992). Hare (1991, 2003) and colleagues developed a reliable and valid clinical instrument for the assessment of psychopathy, the Psychopathy Checklist—Revised (PCL-R). This is a unidimensional observational

scale that quantifies clinical interview and historical data on the patient. Individuals scoring 30 or more on the PCL-R are considered psychopaths for research purposes (Hare 1991, 2003). In our clinical experience, consistent with research, a score in the range of 20–29 would indicate moderate psychopathy, and a score of 30 or higher would indicate severe psychopathy.

Psychopathy is not synonymous with behavioral histories of criminality or a DSM-5 categorical diagnosis of ASPD (American Psychiatric Association 2013; see Box 69–1), although it is often a correlate of both in severe cases. Notably, a substantial body of research has shown that, at most, only one of three individuals in prison with ASPD has severe psychopathy, and those with severe psychopathy have a significantly poorer treatment prognosis than do other antisocial patients with measurably fewer psychopathic traits (Hare 1991, 2003). The measurement of psychopathy and the use of other psychological tests help to delineate subgroups of antisocial individuals who have lower psychopathy scores and higher levels of anxiety, and who may show a better response to treatment (Hodgins 2007; Hodgins et al. 2010; Ulrich and Coid 2010).

Box 69–1. DSM-5 Diagnostic Criteria for Antisocial Personality Disorder

301.7 (F60.2)

A. A pervasive pattern of disregard for and violation of the rights of others, occurring since age 15 years, as indicated by three (or more) of the following:
   1. Failure to conform to social norms with respect to lawful behaviors, as indicated by repeatedly performing acts that are grounds for arrest.
   2. Deceitfulness, as indicated by repeated lying, use of aliases, or conning others for personal profit or pleasure.
   3. Impulsivity or failure to plan ahead.
   4. Irritability and aggressiveness, as indicated by repeated physical fights or assaults.
   5. Reckless disregard for safety of self or others.
   6. Consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations.
   7. Lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another.

B. The individual is at least age 18 years.

C. There is evidence of conduct disorder with onset before age 15 years.

D. The occurrence of antisocial behavior is not exclusively during the course of schizophrenia or bipolar disorder.

ASPD is associated with considerable and complex comorbidity with other psychiatric conditions (Swanson et al. 1994), particularly substance misuse (Robins et al. 1991), and increased mortality through reckless behavior (Black et al. 1996). At least half of those with ASPD have co-occurring anxiety disorders (Goodwin and Hamilton 2003), and a quarter have a depressive disorder (Lenzenweger et al. 2007). The Epidemiologic Catchment Area study found that substance abuse occurred in 83.6% of individuals diagnosed with ASPD (Regier et al. 1990), although subsequent studies have reported prevalence rates of substance use disorders in ASPD ranging from 42% to 95% (Uzun et al. 2006). Co-

morbid Axis I conditions are important to diagnose, because the presence of ASPD acts as a negative moderator of treatment response when these conditions are treated by conventional approaches. Psychopathy appears, however, to be independent of most Axis I conditions, except for alcohol and other substance abuse and dependence (Hart and Hare 1989; Smith and Newman 1990).

Given the action-oriented nature of these patients and the likelihood of head injury, neurological and neuropsychological impairments also must be ruled out. Such impairments may exacerbate clinical expressions, such as the physical violence of this character pathology.

General Treatment Findings

Although the mainstay of treatment for ASPD is psychological therapy, only a small number of high-quality treatment trials have been conducted among people with ASPD, so the evidence base for effective treatments for this patient group continues to be very limited (Duggan et al. 2007; Gibbon et al. 2010; National Institute for Health and Clinical Excellence 2009; Warren et al. 2003). Furthermore, a comparative evaluation of available studies is hampered by different diagnostic criteria and conceptualizations of psychopathy versus ASPD, differences in defining and measuring outcomes, a focus on treating incarcerated patients rather than those in the community, and a focus on behavioral and symptomatic rather than structural personality change.

Programs that have the largest effect sizes adhere to the risk-needs-responsivity model (Andrews 1995). These programs focus on risk (targeting those patients at greatest risk of reoffending), need (empirically established dynamic criminogenic risk factors, such as criminal attitudes, substance abuse, and impulsivity), and responsivity (delivering interventions in a manner that maximizes offender engagement in the treatment process). The effect sizes are typically one-half of the overall effects in meta-analyses of psychological interventions in general (Simon 1998).

A review of the treatment research concerning criminal psychopathic patients, who have the most severe form of ASPD according to the criteria of Hare (2003), has challenged the view that psychopathy per se is always untreatable. Salekin (2002) conducted a meta-analysis of 44 studies of a broad range of correctional treatments with various samples of psychopathic subjects and found an overall positive treatment effect. Lengthier and more intensive treatments—those including an average of at least four sessions per week of individual psychotherapy for at least 1 year—were found to be significantly more effective. However, this review was criticized for including case studies, use of therapist opinion regarding patient change, use of other measures of psychopathy than the PCL-R, and including studies that did not use recidivism as an outcome measure (Harris and Rice 2006). D'Silva et al. (2004) reviewed 10 studies of the treatment of psychopaths with high scores on the PCL-R, and found that although four studies concluded that psychopaths respond poorly to treatment, another four suggested the opposite. A more recent review by Salekin et al. (2010), which included only studies using the PCL-R for diagnosing psychopathy, showed three of eight studies with positive treatment outcomes, whereas treatment of psychopathic youths was more promising, with six of eight studies showing treatment benefits.

Another comprehensive review of the literature on rehabilitating general, psychopathic, and high-risk offenders (Skeem et al. 2009) gives rise to further optimism that intensive, targeted, appropriate psychosocial interventions based on risk-needs-responsivity principles reduce recidivism risk in some severely psychopathic individuals. The reduction in risk is more likely when cognitive-behavioral techniques are applied to address risk for recidivism, and when the treatment relationship between offender and provider is characterized by caring, fairness, and trust as well as an authoritative—not authoritarian—style. Interventions that are punitive or that focus on control and surveillance may increase risk of recidivism if not combined with rehabilitative efforts.

The Dangerous and Severe Personality Disorder (DSPD) initiative in the United Kingdom (Department of Health and Home Office 1999) illustrates the challenges of treating and researching antisocial and psychopathic patients. This ambitious pilot program for the treatment of patients with DSPD—patients assessed as posing significant risk of harm to others and whose risk is linked to their personality disorder—in specialized intensive units in selected prisons and forensic hospitals was established in the United Kingdom in 2001. Although cognitive-behavioral techniques predominated in these treatment programs, some programs also used psychodynamic ideas to both manage staff and tailor therapeutic interventions, such as using the therapeutic community model of treatment. However, despite substantial investment into research and evaluation of the programs, no high-quality trials of specific treatments or service environments were carried out, so the key question as to what treatments are effective for high-risk personality-disordered offenders remains unanswered (Völlm and Konappa 2012). The program has recently been disbanded in favor of a reconfigured national strategy for managing offenders with severe personality disorders based on a "whole systems pathway" across the criminal justice system and National Health Service (Joseph and Benefield 2012).

Treatment Planning

Once the severity of psychopathy has been assessed in the patient with ASPD and any other treatable psychiatric disorders have been identified, four clinical questions should guide further psychiatric involvement with the patient:

1. *Risk assessment:* What are the risks posed by the patient, and is the treatment setting secure enough to contain the relative severity of the psychopathic disturbance in the patient with ASPD?
2. *Personality characteristics and treatment prognosis:* What personality characteristics, gleaned from clinical research on patients with ASPD or psychopathy, are relevant to the treatment planning for this particular patient?
3. *Clinician's reactions to patient:* What are the emotional and/or countertransference reactions that the clinician can expect in himself or herself when attempting to clinically treat or help risk-manage (if no treatment is being attempted) this patient?
4. *Specific treatment approaches:* What specific treatments, if any, should be applied to this patient, given the resources available and the degree of containment necessary to effectively intervene?

Each of these questions is addressed in turn in the sections that follow.

Risk Assessment

An essential component of management of the patient with ASPD is the *setting* in which treatment is delivered, wherein containment, risk, boundaries, and disclosure of information are paramount (Meloy and Yakeley 2010). The treatment setting must be secure enough to ensure the safety of both patients and staff before treatment planning can begin, depending on the available resources. If it is not, staff may be put physically at risk by a decision to commence treatment. Political and bureaucratic pressures may be brought to bear on clinicians to "treat" currently untreatable patients with ASPD and severe psychopathy, and a "not-to-treat" decision may entail a variety of personal and professional dilemmas.

By far the most troublesome symptom of ASPD is violence, which is significantly more frequent in the severely psychopathic patient (Hare and McPherson 1984). Reis (1974) labeled "affective" and "predatory" aggression, and Eichelman (1992), Meloy (1988, 1997, 2006), McEllistrem (2004), Siegel and Victoroff (2009), Siever (2008), and others have elaborated upon the physiological, pharmacological, and forensic distinction between the two types. These psychobiologically different modes of violence are most relevant to ASPD and psychopathy, although they are not inclusive and should not be considered a standardized clinical nosology for aggression (Eichelman and Hartwig 1993). Affective (emotional, reactive) aggression is a mode of violence that is accompanied by high levels of sympathetic arousal and emotion (usually anger or fear) and is a reaction to an imminent threat. Predatory (instrumental) aggression is a mode of violence that is accompanied by minimal or no sympathetic arousal and is emotionless, planned, and purposeful. Research has shown that psychopathic criminals are more likely than other criminals to engage in both affective and predatory violence (Cornell et al. 1996; Serin 1991; Walsh 1999; Williamson et al. 1987; Woodworth and Porter 2002). Blair et al. (2005) noted that "no biologically based disorder other than psychopathy is associated with an increased risk of instrumental aggression" (p. 155).

Psychopathic criminals are typically three to five times more violent than nonpsychopathic criminals (Hare 2003), but even the most violent patients are not violent most of the time. Measurement of violence risk in both psychiatric and offender populations has found that psychopathy typically accounts for the largest proportion of explainable variance. We recommend such instruments as the Violence Risk Appraisal Guide (VRAG; Quinsey et al. 2006), the Classification of Violence Risk (COVR; Monahan et al. 2005), the HCR-20 Version 3 (Douglas et al. 2013), and the PCL-R. Yang et al. (2010) have found, however, that most actuarial and structured professional judgment instruments are equivalent in their moderately accurate prediction of violence risk, and should instead be selected on the basis of specific relevance to the patient's history of violence. All risk-of-violence evaluations should be individualized and will benefit from a complete biopsychosocial understanding of the patient.

Personality Characteristics and Treatment Prognosis

Anxiety and Attachment

Hodgins and colleagues emphasize the importance of co-occurring anxiety in

subtyping ASPD (De Brito and Hodgins 2009). Based on studies of children and adults, they propose that around half of individuals in the ASPD population are characterized by anxiety as well as persistent antisocial behavior, and have low levels of callous unemotional traits as children and low levels of psychopathic traits as adults. This group is more likely to have experienced physical abuse as children and resort to violence as a compensatory response to underlying emotional conflict and distress. The other half have normal to low levels of anxiety and varying levels of psychopathy, but include a subgroup with high levels of psychopathy. This group shows marked callous and unemotional traits as children, low levels of anxiety, more predatory (instrumental) violence, and less amenability to treatment. There is also suggestive research that severely psychopathic adults experienced *less abuse and neglect* as children than moderately psychopathic adults, which also supports the relative increase in biogenic contributions as degree of psychopathy increases (Felthous and Sass 2007; Raine 2013).

Anxiety is a necessary correlate of any successful mental health treatment that depends on interpersonal methods, because it marks a capacity for internalized object relations and may signal other affects. As the severity of psychopathy increases in patients with ASPD, anxiety likely lessens, and with it the personal discomfort that can motivate a patient to change.

Attachment, or the capacity to form an emotional bond, is considered to be lower in severely psychopathic criminals than in mild to moderately psychopathic criminals (Fonagy et al. 1997; Frodi et al. 2001; Gacono and Meloy 1994; Levinson and Fonagy 2004; Meloy 2002; van IJzendoorn et al. 1997). For a patient without an attachment capacity, any treatment that depends on the emotional relationship with the psychotherapist will fail and may pose an explicit danger to the professional because a lack of empathy for the therapist will not inhibit aggression. The more severe the psychopathy, the more the patient will relate to others on the basis of power rather than affection (Meloy 1988).

Narcissism

Psychopathic patients can be conceptualized as aggressive narcissists, with the attendant intrapsychic object relations, structure, and defenses that have been described in the psychoanalytic literature (Kernberg 1992; Meloy 1988). In a clinical and treatment setting, the more severe the psychopathic disturbance in the patient with ASPD, the greater the likelihood that aggressive devaluation will be used to shore up feelings of grandiosity and repair emotional wounds. In some patients, this devaluation is defensive, whereas in others, a core, injured sense of self is not apparent. This behavioral denigration of others can run the clinical spectrum from subtle verbal insults to the rape and homicide of a female staff member. It also distinguishes the psychopathic patient from the narcissistic patient, who can devalue in fantasy (Kernberg 1975) without resorting to the infliction of emotional or physical pain on others.

In addition to the devaluation of others, the severity of psychopathy will determine the degree to which the patient will try to control other patients and staff. This "omnipotent control" in the actual clinical setting, often felt by staff as being "under the patient's thumb" or "walking on eggshells," usually serves the purpose of stimulating the severe psychopath's grandiose fantasies and also warding off the patient's fears of being controlled by malevolent forces outside

himself or herself. When the grandiosity of the mildly to moderately psychopathic patient with ASPD is challenged by failure, there will be clinical manifestations of anxiety or depression, both of which are positive prognostic indicators (Gabbard and Coyne 1987).

Psychological Defenses

ASPD patients with severe psychopathy most predictably use the following psychological defenses: projection, devaluation, denial, projective identification, omnipotence, and splitting (Gacono and Meloy 1994; Hare 2003). For instance, projective identification is most apparent in treatment when the psychopathic patient attributes certain negative characteristics to the clinician and then attempts to control the clinician, perhaps through overt or covert intimidation. An aspect of the psychopathic patient's personality is then perceived in the clinician and viewed as a threat that must be diminished. Higher-level or neurotic defenses, such as idealization, intellectualization, isolation, sublimation, and repression, appear to be virtually absent in the patient with ASPD and severe psychopathy (Gacono 1990). If neurotic defenses are present in the patient with ASPD, they suggest amenability to treatment.

Object Relations

The severely psychopathic patient's internal representations of self are aggressive and larger than life—this person is a legend in his or her own mind. At the same time, this patient does not consider others as whole, real, and meaningful individuals deserving of respect and empathy, but instead as objects to dominate and exploit. Patients with ASPD without severe psychopathy may see themselves as injured or devalued, and their grandiosity may be defensive and easily punctured.

The treatment implications of these object relations surround the risk of violence by patients with ASPD. The more psychopathic these individuals are, the more pleasurable, less conflicted, and more sadistic their aggressive acts will be (Dietz et al. 1990; Holt et al. 1999). The psychopathic patient may wholly identify with the aggressor (A. Freud 1936/1966) and have no inhibitions. A history of violence, coupled with the predatory (instrumental) nature of their violence, makes ASPD patients with severe psychopathy very dangerous in a hospital milieu without appropriate security (Gacono et al. 1995, 1997).

Affects

The emotions of the patient with ASPD lack the subtlety, depth, and modulation of those of psychiatrically healthy individuals. The patient with ASPD and severe psychopathy appears to live in a "presocialized" emotional world, where feelings are experienced in relation to the self but not to others. Such a patient is unlikely to have a capacity to experience emotions such as reciprocal pleasure, gratitude, empathy, joy, sympathy, mutual eroticism, affection, guilt, or remorse, that depend on whole object relations. The patient's emotional life instead is dominated by feelings of anger, sensitivities to shame or humiliation, envy, boredom, contempt, exhilaration, and pleasure through dominance (sadism).

Such feelings in the patient with ASPD and severe psychopathy pose difficulties for modalities that depend on emotional access to the patient, such as cognitive-behavioral relapse prevention or psychodynamic approaches that require the patient to have a capacity to feel emotion in relation to the psychotherapist and to talk about it. Most troublesome and difficult to detect is the psy-

chopathic patient's imitation of certain emotional states for secondary gain or to manipulate the psychotherapist.

Superego Pathology

The touchstone of psychopathy and ASPD has been the absence of conscience, or serious deficits in moral judgment (Cleckley 1941/1976; Hare 1991; Johnson 1949; Robins 1966). Although few controlled studies of moral development in psychopathy have been done (Hare 2003; Trevethan and Walker 1989), clinicians agree that this characteristic is a marker for the character pathology (Kernberg 1984; Meloy 1988; Reid et al. 1986).

The presence of any superego development, whether a prosocial ego ideal (a realistic, long-term goal) or clinical evidence of a socially desirable need to rationalize antisocial acts, is a positive prognostic sign. Certain mild to moderately psychopathic patients with ASPD may show evidence of harsh and punitive attitudes toward the self and assume a masochistic attitude toward the clinician. This behavior signifies some internalized value and attachment capacity. ASPD patients with severe psychopathy are likely to behave cruelly toward others and show no need to justify or rationalize their behaviors. Such individuals should not be considered for a treatment setting because they place both staff and other patients at risk.

Clinician's Reactions to Patient

Lion (1978), Symington (1980), Strasburger (1986), Meloy (1988, 2001), and Gabbard (2014) explored the clinician's response to the patient with psychopathy or ASPD. Table 69–1 lists nine common countertransference reactions to such a patient. These reactions, each of which is discussed in the following subsections, are likely to occur regardless of the treatment modality being applied and will be felt more intensely when psychopathy is more severe in the patient with ASPD. These are reactive emotions and thoughts and should not be construed as necessarily implicating a conflict in the clinician. Such subjective reactions can be used as an impetus for further objective testing, a reevaluation of the appropriateness of the selected treatment, or in some cases the cessation of treatment.

TABLE 69–1. Common countertransference reactions to the patient with antisocial personality disorder

1. Therapeutic nihilism
2. Illusory treatment alliance
3. Fear of assault or harm
4. Denial and deception
5. Helplessness and guilt
6. Devaluation and loss of professional identity
7. Hatred and the wish to destroy
8. Assumption of psychological maturity
9. Fascination, excitement, or sexual attraction

These countertransference reactions are most readily explored in individual or group supervision or in carefully led clinical staff meetings in which a wide range of emotional reactions toward patients are tolerated and accepted. Clinicians who are resistant to any understanding of their own emotional lives in relation to these patients should not be treating them and may put other mental health professionals at risk.

Therapeutic Nihilism

Lion (1978) used the term *therapeutic nihilism* to describe the clinician's rejection of all patients with an antisocial history as being completely untreatable. Instead of arriving at a treatment decision based on a clinical evaluation, including an assessment of the severity of psychopathy, the clinician devalues the patient as a member of a stereotyped class of "untouchables." The clinician does to the patient with ASPD what the patient does to others.

Illusory Treatment Alliance

The opposite of therapeutic nihilism is the illusion that there is a treatment alliance when, in fact, there is none. Perceptions of such an alliance are often the psychotherapist's own wishful projections. Behaviors by a severely psychopathic patient that suggest such an alliance should be viewed with clinical suspicion and may actually be imitations to please and manipulate the psychotherapist. The chameleon-like quality of the psychopathic patient is well documented (Greenacre 1958; Meloy 1988, 2001). Bursten (1973) elaborated on the "manipulative cycle" of the psychopathic patient, which leads to a feeling of contemptuous delight in these patients when successfully carried out. The clinician is left with feelings of humiliation and anger.

Fear of Assault or Harm

Strasburger (1986) noted that both reality-based and countertransference fears may exist in response to the ASPD patient with severe psychopathy. Real danger should not be discounted and is most readily evaluated by using contemporary measures to assess the risk of violence (Monahan et al. 2001). Countertransference fear is an atavistic response to the psychopathic patient as a predator and may be viscerally felt as "the hair standing up on my neck" or the patient "making my skin crawl." These are phylogenetically evolved autonomic reactions that may also signal real danger, even in the absence of an overt threat. They appear to be widespread among clinicians working with psychopathic patients (Meloy and Meloy 2002).

Denial and Deception

Denial in the psychotherapist is most often seen in counterphobic responses to real danger. Lion and Leaff (1973) suggested that such denial is a common defense against anxiety generated by violent patients. It may also be apparent in the unwillingness of mental health clinicians to participate in the prosecution of a psychopathic patient who has seriously injured someone (Hoge and Gutheil 1987), in the underdiagnosis of ASPD (Gabbard 2014), or in clinicians' disbelief that the patient has an antisocial history (Symington 1980) or that psychopathy even exists at all (Vaillant 1975). This reaction may lead to splitting or contentiousness among mental health staff, especially in hospital settings.

In our clinical experience, deception of the patient with ASPD is most likely to occur when the psychotherapist is frightened of the patient, especially of the patient's rage if certain limits are set surrounding treatment. It may also indicate

superego problems in the clinician, the avoidance of anxiety, passive-aggressive rejection of the patient, or an identification with the deceptive skills of the patient with ASPD. Rigorous honesty without self-disclosure is the treatment rule in working with patients with ASPD.

Helplessness and Guilt

In our experience, the novice clinician may especially feel helpless or guilty when the patient with ASPD does not change despite treatment efforts. These feelings may originate from the psychotherapist's narcissistic belief in his or her own omnipotent capacity to heal, what Reich (1951) called the "Midas touch syndrome."

Devaluation and Loss of Professional Identity

If therapeutic competency is measured only through genuine change in the patient, the patient with ASPD will be a source of continuous professional disappointment and narcissistic wounding. In long-term treatment, the psychopathic patient's intransigence may compel the clinician to question his or her own professional identity. Bursten (1973) noted that despite the psychotherapist's most adept management of the patient's contempt, it is difficult not to feel despicable and devalued because of the primitive, preverbal nature of the patient's manipulative cycle. The clinician's emotional responses to the patient may range, in this context, from retaliation and rage to indifference or submission.

Hatred and the Wish to Destroy

One psychiatric resident recalled the embarrassing dream of being with a hospitalized patient with ASPD whom he was treating as they both stormed through the hospital with flame throwers, destroying everything in sight. No other patient will compel psychotherapists to face their own aggressive and destructive impulses like the psychopath will. Because these patients often hate goodness itself and will destroy any perceived goodness (such as empathy) offered by the clinician, the clinician may react by identifying with the patient's hatred and wish to destroy. It may become a source of understanding and relating to the patient if brought into consciousness (Gabbard 1996; Galdston 1987).

Assumption of Psychological Maturity

The most subtle countertransference reaction is the clinician's belief that the patient with ASPD is as developmentally mature and complex as the clinician, and that the patient's actual maturity only has to be facilitated by, and discovered in, treatment. This is particularly common when no other psychiatric disorder is present and the patient has an above-average IQ.

Fascination, Excitement, or Sexual Attraction

Some clinicians are strongly drawn to patients with ASPD or psychopathy, and provide an eager audience for these patients to regale with their prowess and exploits. Such an idealizing countertransference can also be sexualized, which may invite an exceedingly dangerous encounter, especially between a male patient with psychopathy and a female psychotherapist. Young mental health professionals will often be enamored with criminal forensic work for the sensation seeking that it promises and the un-

conscious identifications with psychopathy that it invites. What is forbidden is often what is most desired. If clinicians come to understand the fantasized extremes of their own aggressive and hedonistic desires, this fascination will often devolve into more realistic boredom, and then the clinical task becomes maintaining interest in a patient who offers little hope for change (Meloy and Reavis 2006). In one study of malingering insanity acquittees (N=18) in a large forensic hospital, most were severely psychopathic and 39% had a consensual sexual relationship with or married a female staff member (Gacono et al. 1995).

Specific Treatment Approaches

Although cognitive-behavioral and social learning techniques are the most frequently used methods for treating individuals with ASPD, there is a renewed interest in applying psychodynamic treatments for ASPD, such as a therapeutic community approach or mentalization-based treatment. Although a standardized assessment instrument such as the PCL-R should be used to measure psychopathy accurately, clinical indicators of the *absence* of severe psychopathy in the patient with ASPD include the "ABCs" of anxiety, bonding, and conscience. The effectiveness of a modality will depend on the treatment goals, which should be conservative at best.

Pharmacotherapy

Recent treatment recommendations caution against pharmacological treatment of the primary traits of ASPD. Two large meta-analyses of trials for pharmacological interventions for ASPD (Khalifa et al. 2010; National Institute for Health and Clinical Excellence 2009) concluded that there was no consistent evidence, including that from uncontrolled studies, that supported use of any pharmacological intervention to treat the disorder or the underlying behavior and symptoms of the disorder. The authors recommended that pharmacological interventions should not be routinely used for the primary treatment of ASPD or associated behaviors of aggression, anger, and impulsivity, but should be used only for the treatment of comorbid mental disorders, in particular depression and anxiety (National Institute for Health and Clinical Excellence 2009). The authors also highlighted the importance of paying attention to issues of adherence and the risks of misuse or overdose.

Family Therapy

There is increasing interest in the prevention of ASPD by targeting early interventions at individuals and families at risk of developing the condition (e.g., Brotman et al. 2007, 2008). Programs involving preschool nursery, schools, and home visiting have been shown to be effective in preventing conduct disorder in children of high-risk parents. Parent training programs and cognitive problem-solving programs may be effective for preadolescent children with conduct disorder; however, for teenage children with conduct disorder, programs need to be augmented by other interventions such as functional family therapy, systemic family therapy, multisystemic therapy, or multidimensional treatment foster care (National Institute for Health and Clinical Excellence 2009).

Virtually no published research is available on family therapy with adult parents who have ASPD, whether psychopathic or not. The use of family therapy when one of the participating adults is a

severely psychopathic patient with ASPD is not advised. Information learned by the individual from both the therapist and other family members is likely to be used to hurt and control in the service of sadism and omnipotent fantasy (Meloy 1992). Treatment efforts should focus on the physical, economic, and emotional safety of the other family members, whether spouse, children, or elderly parents; such efforts should also play an important role in custody litigation to help mitigate the intergenerational transmission of such problems.

Mild to moderately psychopathic adults with ASPD may benefit from family therapy and are most likely to be seen when a child with conduct disorder is the identified patient. Such work may also have a positive effect on the intergenerational transmission of the disorder, a likely combination of both early social learning and psychobiology (Sutker et al. 1993). Reductions in criminal recidivism as a result of family therapy have been reported (Gendreau and Ross 1987).

Milieu and Residential Therapy

The term *milieu* is used to describe any treatment method in which control of the environment surrounding the antisocial individual is the primary agent for change. Two milieu or residential approaches have been used for the treatment of ASPD: token economies and therapeutic communities.

Token economies have been empirically found to shape patient and staff behavior within institutions (Rice et al. 1990). A token economy is a system of behavior modification based on the principles of operant conditioning and the systematic positive reinforcement of target behavior. The reinforcers are symbols or tokens that can be exchanged for other reinforcers. Despite their declining popularity, token economies have no serious competition as a system of behavioral management in hospitals. Evidence also indicates that the more typically unstructured hospital ward may actually harm patients by promoting psychotic, aggressive, and dependent behaviors (Positano et al. 1990).

Therapeutic residential communities use peer influence as the key agent of change to help individuals acquire social skills and learn social norms. Although no trials of therapeutic communities have been reported specifically for ASPD, there are studies investigating the efficacy of therapeutic communities for general offenders in institutional and community settings. Most, however, are based on weak study designs. Lamb and Goertzel (1974) conducted a randomized controlled trial (RCT) that investigated a community alternative to prison in the United States, and prospective (Robertson and Gunn 1987) and retrospective (Marshall 1997) cohort studies have investigated the effects of therapeutic communities for prisoners treated in HM Prison Grendon in the United Kingdom. None of these studies revealed evidence to suggest that therapeutic communities were effective for general offenders. However, three well-designed RCTs have been conducted in institutional settings evaluating the evidence for therapeutic communities in substance misuse offenders (Nielson et al. 1996; Sacks et al. 2004; Wexler et al. 1999). All three studies found a relatively large reduction in reoffending. Up to half of the trial subjects were diagnosed with ASPD, and all participants reported behavior or symptoms associated with the ASPD diagnostic construct. These findings have led to the conclusion that therapeutic communities are only effective for treating ASPD if they are targeted specifically at those individuals with comor-

bid drug misuse (National Institute for Health and Clinical Excellence 2009), and there is insufficient evidence to apply these findings to therapeutic communities targeting general offenders who do not abuse substances. However, in our opinion, given that many of the previous studies were based on weak methodology and, moreover, that up to 90% of individuals with ASPD may misuse substances, it is premature to conclude that therapeutic communities are ineffective for the treatment of ASPD in general. Enthusiasm for the model persists, and in the United Kingdom there are currently plans to extend the availability of therapeutic community treatment of high-risk offenders in prisons (Joseph and Benefield 2012).

Cognitive-Behavioral Therapy

Cognitive-behavioral techniques have been developed into specific treatment programs that have been shown to have some success in offenders with personality disorders, which are likely to include many diagnosed with ASPD. These techniques include relapse prevention programs (Andrews et al. 1990); programs combining cognitive skills with social skills and problem solving, such as Reasoning and Rehabilitation and Enhanced Thinking Skills (Friendship et al. 2002); anger and violence management programs (Saunders 1996; S. Wong and A. Gordon, The Violence Risk Scale, 2000); sex offender treatment programs (Beech et al. 1999, 2001); and treatments for psychopathic individuals (Wong and Hare 2005). Group-based cognitive-behavioral approaches may be the most effective (National Institute for Health and Clinical Excellence 2009). There is also some recent evidence for the effectiveness of cognitive-behavioral therapy in reducing antisocial behaviors and changing thinking for individuals in the community with a diagnosis of ASPD (Davidson et al. 2009).

Patients with ASPD are likely to respond to treatment if they are motivated to change and if therapy is used in a milieu or residential setting. Treatment response is most predictable in the moderately psychopathic patient with ASPD who normatively responds to aversive consequences and has felt the emotional and practical pain of his or her antisocial acts. Treatment is unlikely to have any effect on the severely psychopathic patient with ASPD because of deficits in passive avoidance learning (inhibiting new behavior when faced with punishment), the inability to foresee the long-term consequences of his or her actions, and the lack of capacity to reflect on the past.

Wong and Hare (2005) have devised guidelines for psychopathic treatment programs that are based on the risk-needs-responsivity principles (Andrews 1995) mentioned earlier in this chapter in the section "General Treatment Findings." These guidelines recommend cognitive-behavioral methods of treatment based on a modified social information processing model and the demonstrated efficacy of relapse prevention (Dowden et al. 2003). Wong and Hare (2005) argue that resources are better utilized when directed at high-risk offenders and when they target dynamic factors directly linked to criminality and violence. They spurn attempts to change the character pathology or temperament of the psychopath. A study on psychopathic individuals in an intensive high-risk sex offender program (Olver and Wong 2009) and a similar study with serious high-risk violent offenders (Olver et al. 2013) showed not only that there was progress on risk-related treatment targets but also that the more the offenders

changed, the fewer sexual and violent reconvictions they had.

When severely psychopathic individuals are ordered into forensic hospitals by the courts, strict behavioral controls should be used to manage behavior, and any clinical improvement should be viewed with great skepticism. All judicially committed patients, whether inpatient or outpatient, should be assessed for degree of psychopathy given the power of the construct to predict treatment outcome and violence risk (Hare 2003).

Psychodynamic Approaches

No evidence to date indicates that patients with psychopathy or ASPD benefit from traditional psychodynamic psychotherapy, including the expressive or supportive psychotherapies (Kernberg 1984), psychoanalysis, or various psychodynamically based group psychotherapies. Forensic psychotherapists working from a psychoanalytic perspective advocate modifications of technique in both individual and group treatments of violent and antisocial offenders. These changes include actively fostering the therapeutic alliance by avoiding silence and free association, focusing on affect and interpretations of the "here and now" rather than on unconscious conflicts and fantasies or on the transference, and using mentalization techniques such as helping the patient to connect internal states of mind to his or her behavioral actions (Meloy and Yakeley 2010; Yakeley 2010).

Forensic psychotherapy has promoted applying to antisocial offenders specific therapies that have been developed and empirically supported for the treatment of severe personality disorders. Although based on different theoretical models, such therapies include both cognitive and dynamic components. Dialectical behavior therapy (Linehan 1993), a variant of cognitive-behavioral therapy, is currently being evaluated for use with women in prisons in England and Wales. Schema-focused therapy (Young et al. 2003), an integrative therapy that brings together elements of cognitive therapy, behavioral therapy, object relations, and gestalt therapy, has been used to treat distorted antisocial cognitions in psychopathic offenders as part of a multimodal treatment program in the criminal justice system in the Netherlands (Chakhssi et al. 2010).

Mentalization-based therapy (MBT) is a psychodynamic treatment approach that integrates cognitive and relational components of therapy and has a theoretical basis in attachment theory. Trials of MBT, which have been shown to be effective for patients with borderline personality disorder (Bateman and Fonagy 1999, 2001, 2008), have included patients with ASPD. In a trial comparing MBT with structured clinical management (SCM), which included problem-solving and social skills, MBT was found to be more effective than SCM in patients with ASPD, but the effectiveness of each treatment was reduced when compared with patients without ASPD (Bateman and Fonagy 2009). MBT for ASPD targets mentalizing problems through a program of group and individual psychotherapy. A recent pilot project of MBT for violent men with a diagnosis of ASPD showed that treatment leads to a reduction in aggressive acts (McGauley et al. 2011), and plans are under way for a multi-site RCT in the United Kingdom.

Finally, psychodynamic treatment of ASPD should be differentiated from psychodynamically *understanding* the patient with ASPD. Psychodynamic understanding of the patient with ASPD (Clarkin et al. 2010; Meloy 1988) assumes that unconscious determinants play a major role in behavior. It also embraces a "levels"

(Stone and Dellis 1960) approach to both understanding and treating personality disorder. In other words, treatment efforts target, or at least acknowledge, the multiple and simultaneous levels that influence observable clinical behavior: psychobiology, unconscious psychodynamics, conscious thought, the situation, and the environment. In the case of a patient with ASPD, this conceptualization could translate into psychopharmacological intervention to minimize depression (psychobiology), the process of thinking about and discussing with staff the aggressive narcissism of the patient and its countertransference effect (psychodynamics), active treatment of the patient with relapse prevention that focuses on the internal and external motivators for antisocial acts (conscious thought), and the choice of a maximum-security milieu treatment program within which the treatment occurs (situation and environment).

Conclusion

Treatment and management of ASPD test the clinician's mettle. Although patients with ASPD rarely seek medical care for their personality disorder—only one out of seven will ever discuss their symptoms with a doctor (Robins et al. 1991)—concurrent problems may bring them into treatment, whether voluntarily or not.

The comprehensive care of the patient with ASPD involves six principles, which require that mental health professionals do the following:

1. Determine, during the initial diagnostic workup, the severity of psychopathy of the patient with ASPD, with a clinical focus on the presence of anxiety, bonding, and conscience.
2. Identify any treatable conditions, such as other mental or substance use disorders.
3. Delineate situational and environmental factors that may be aggravating or worsening the antisocial behaviors.
4. Recognize the likelihood of legal problems and potential legal entanglements, even if the patient initially denies them.
5. Begin treatment only if it is demonstrably safe and effective for both the patient and the clinician. This would generally rule out any attempts to psychiatrically treat the severely psychopathic antisocial patient with any brief, traditional treatment modality. Medical treatment of such a patient's major mental disorder, if present, will usually result in better organization of the psychopathy and may create an increased risk of predatory (instrumental) violence.
6. Pay careful attention to all countertransference reactions, because they provide important insights into the inner world of the patient with ASPD and the severity of his or her psychopathy.

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CHAPTER 70

Borderline Personality Disorder

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The understanding and treatment of borderline personality disorder (BPD) continue to evolve (Gunderson 2009). Patients with BPD were originally conceptualized as having a severe form of intrapsychic personality organization (Kernberg 1967). This proposed understanding of internal organization encouraged the original tide of therapeutic enthusiasm, but long-term, intensive, psychoanalytically informed treatments, though broadly endorsed, were only rarely feasible. Subsequently, a significant literature documented the difficulties encountered with these treatments.

The borderline construct was modified at the time it was redefined as a syndrome with reliably identifiable and discriminating criteria. In 1980, BPD was adopted into the official classification, DSM-III (American Psychiatric Association 1980), as a specific type of personality disorder, taking its place beside others. Box 70–1 lists the DSM-5 criteria for BPD (American Psychiatric Association 2013).

Box 70–1. DSM-5 Diagnostic Criteria for Borderline Personality Disorder

301.83 (F60.3)

A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Frantic efforts to avoid real or imagined abandonment. (**Note:** Do not include suicidal or self-mutilating behavior covered in Criterion 5.)
2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.

3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). (**Note:** Do not include suicidal or self-mutilating behavior covered in Criterion 5.)
5. Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior.
6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

Research has demonstrated that BPD is highly prevalent across all treatment sites (Gunderson and Links 2008) and that patients with BPD are heavy utilizers of health care services (Bender et al. 2001; Sansone et al. 2011). At this point, the BPD construct includes a significant core heritability (Gunderson et al. 2011). The onset of BPD is usually in early adolescence, and its subsequent course involves a generally favorable rate of remission but with persistent social disabilities. BPD is the only personality disorder with 1) effective disorder-specific treatments and 2) a course that dominates the outcome of most co-occurring disorders. In retrospect, the earlier literature indicating how difficult these patients are to treat is now interpreted as representing how treatments that do not accommodate the specific needs of these patients will often make them worse. Noncompliance, dropping out, psychotic transferences, regressions, escalating self-destructiveness, and escalating hospital usage should be seen as signs of ineffective treatments rather than as signs of an untreatable patient.

Despite the availability of effective treatments, the treatments received by patients with BPD remain wildly inconsistent and are often harmful. Some problems relate to stigma, lack of training, and misinformation. Three widely prevalent clinical failures are 1) *misdiagnosis*—not appropriately giving the BPD diagnosis while offering others (most frequently major depressive disorder [MDD] or bipolar disorder), which leads to unrealistic expectations and ineffective medications, which in turn prompt unnecessary despair and beget unnecessary chronicity; 2) *excessive reliance on medication*—even when BPD is diagnosed, treatments often rely too heavily on medications, which inherently mislead these patients away from their need, and their capability, to proactively learn to take better control of themselves; and 3) *inadequate psychoeducation*—patients and families are rarely provided with knowledge about this disorder's origins, course, and treatment. This failure unwittingly but destructively enables the persistence of bitter and costly unrealistic expectations, blaming, and inadequate future planning.

In this review of BPD treatment, we describe the common characteristics of effective treatments, discuss the distinctions between them, identify the role of different modalities and of various levels of care, and end with some summarizing conclusions. As in previous editions of this chapter, we emphasize empirically supported practices and attempt to identify those recommended practices that are based on our clinical experience. Some treatment studies are not discussed (Gunderson and Links 2008; I. Weinberg, "Evidence-Based Psychological Treatments of Borderline Personality Disorder

Patients," unpublished manuscript) because we concluded that they had not yet gained sufficient visibility to affect clinical practices.

General Principles of Effective Therapies

Starting in the 1990s, the view of BPD's treatability has been transformed by several evidence-based treatments (EBTs) that uniformly documented efficacy when compared to usual care (i.e., treatment as usual) (Bateman and Fonagy 2003; Linehan et al. 2001, 2006). These trials demonstrated significantly decreased suicidality, self-harm, and depression, as well as dramatically decreased usage of hospitals, emergency rooms, and medications. As we discuss in the next section, although these and other EBTs have distinctive theories and forms of intervention (e.g., Clarkin et al. 2007; Giesen-Bloo et al. 2006), the similarity of their outcomes has drawn attention to the overriding significance of their commonalities (Bateman 2012; Gabbard 2007; Gunderson 2011; Weinberg et al. 2011).

Basic guidelines for clinicians in all settings and with all modalities can be derived from those characteristics that all of the empirically validated treatments of BPD have in common. These are summarized below.

Structure

The treatment framework needs to be as clear and stable as possible.

1. A primary clinician needs to be identified. This treater organizes treatment, monitors progress, oversees safety, and makes decisions about changes.
2. Goals and roles need to be clarified. It may be a goal in itself to establish more specific goals, such as decreasing self-injury or anger, but there needs to be agreement regarding general goals, such as improving communications, understanding oneself, or getting a better life. Therapists need to be clear about what can and cannot be expected from them. Specifically, they need to be clear about their availability and possible use for interceding with self-endangering or suicidal impulses. They also need to be clear about their limitations, such as their inability to read minds or to anticipate and prevent bad things from happening.

Support

Concerned attention is a nonspecific part of good treatments that is essential. The following are more specific forms of support.

1. *Validation*—A clinician should convey appreciation for a patient's extreme distress and desperation but must be cautious about validating patients' perceptions of others. Such perceptions may be accurate, but they are often biased by misperceptions—for better or worse—of others' motives and feelings.
2. *Encouragement*—As part of basic psychoeducation given to all patients with BPD (and their families), the clinician should provide encouragement regarding the patients' prospects for improvement and the ability to change.

Involvement

Patients with BPD are very sensitive to signs that treaters are angry, scared, or otherwise rejecting. These patients experience nonresponsiveness as neglect or even hostility.

1. The therapy relationship is dyadic. Clinicians need to engage with patients who have BPD as "real people" while at the same time limiting self-disclosures only to what will facilitate a patient's trust and alliance.
2. Clinicians need to be active but nonreactive. Being active includes challenging patients' silences, digressions, or superficiality. At the same time, clinician responses need to be measured and contained, and to model reflectiveness, self-awareness, and curiosity. Expressions of concern about self-endangering behaviors need to be accompanied by judicious inquiries and by not overreacting.

Connecting of Acts and Feelings to Events

Connecting acts and feelings to events is an essential task within all treatments. It reflects what is thought to be the BPD patient's developmental failure to learn to identify emotions or impulses and to see their relationship to preceding events. This focus is particularly valuable in here-and-now situations (including angry or dismissive responses). Helping patients connect their feelings to rejection, lost supports, and other interpersonal events is crucial. Within hospital, residential, and partial hospital settings, it is unfortunately easy to lose sight of BPD patients' precipitating social stressors.

Monitoring and Discussion of Countertransference

Treaters need to be self-aware and to be ready to consult with colleagues. They need to recognize that idealization or devaluation is the patient's interpersonal style. Clinicians can take these attributions personally. Clinicians also need to recognize that inclinations to rescue or reject patients with BPD are predictable reactions (countertransferences) that can disrupt treatment and may require outside consultation. Discussing one's reactions and interventions with colleagues reduces burden, leads to valuable support, and safeguards against liability. Countertransference can also be an important source of information regarding the patient's internal state and the nature of the patient-therapist relationship—knowledge that can help in promoting attachment and addressing problematic relational patterns.

Evidence-Based BPD-Specific Psychotherapies

Randomized trials have supported the efficacy of several forms of psychotherapy for patients with BPD. As noted earlier, all have shown similar effectiveness in reducing the following: hospital, emergency room, and medication utilization; suicidality and self-harm; and depression. Characteristically, these treatments involve 2–3 hours per week of outpatient care for 1 or more years. Therapists are self-selected psychiatrists or psychologists who have received fairly extreme and specific training until they achieve competence. In addition, they then have ongoing supervision during the trials. In this section, we describe four of these EBTs (listed in Table 70–1 as "supported"), which we selected because 1) they are designed to treat the whole personality disorder (not just facets), 2) randomized controlled trials (RCTs) have reported their efficacy at least twice, and 3) training opportunities have been developed so that the practice of these treatments can be expected to expand. Other evidence-based psychotherapies for BPD (e.g., gen-

eral psychiatric management [McMain et al. 2009], schema-focused therapy [Giesen-Bloo et al. 2006], cognitive-behavioral therapy [Davidson et al. 2006], cognitive analytic therapy [Chanen et al. 2008]) may yet attain these measures of potential growth and will then deserve equal attention. At present they are identified in Table 70–1 as "promising."

The four types of EBT described below have been outlined in manuals so that therapists' adherence to the particular approach can be reliably assessed. Follow-up studies have shown that the clinical and cost benefits are maintained during a period of 2–5 years. However, in part because extensive training is required to deliver these therapies, they are still not widely available.

Dialectical Behavior Therapy

Linehan (1993a) developed dialectical behavior therapy (DBT) specifically for patients with BPD. She hypothesized that the primary impairment in patients with BPD is a constitutional dysregulation of emotion interacting with an invalidating environment. The empirical support for DBT's efficacy, the rigor and feasibility of attaining training, and the clarity of its implementation have inspired increasingly widespread use of this modality. DBT includes manualized group and individual therapy components (Linehan 1993b); the group therapy focuses on teaching patients behavioral coping skills, whereas the individual therapy focuses on "coaching" patients to attain the following six goals for change that are arranged with hierarchical priority: 1) suicidal behaviors, 2) therapy-interfering behaviors, 3) behaviors that interfere with quality of life, 4) behavioral skill acquisition, 5) posttraumatic stress behavior, and 6) self-respect behaviors.

The individual therapists are on call for crises, which prompt coaching of patients in use of skills. In contrast, psychodynamic therapies have tended to view suicidality and self-destructiveness as symptoms that will subside after underlying problems resolve. An important aspect of DBT is its use of a "consultation group." The group's co-therapists and the individual therapist meet weekly to help one another maintain a balance between acceptance and a call for change. Also, as per general principle 5 (see the earlier section "General Principles of Effective Therapies"), these group meetings help to monitor and guard against clinician burnout related to the interpersonal strains of working with patients who have BPD (i.e., countertransference reactions).

Some of the initial DBT trial's effectiveness has been confirmed in an outpatient trial in which DBT was compared with community treatment by "expert" clinicians (Linehan et al. 2006). DBT's effectiveness has also been confirmed in inpatient (Bloom et al. 2012) and correctional settings (Robins and Chapman, 2004). Adaptations of DBT have been made for samples of patients with eating disorders (Bankoff et al. 2012), substance use disorders (Dimeff and Linehan, 2008), and posttraumatic stress disorder (Harned et al. 2012), as well as suicidal adolescents with BPD (Klein and Miller 2011); the modified versions of DBT have been effective in reducing the respective target behaviors.

The approach developed by Linehan (1993a) testifies to the importance of making adaptations to usual behavior therapies. Specifically, like the dynamic therapies of the Adler/Kohut type, Linehan's DBT emphasizes the role of validation and empathy. Moreover, developing and maintaining the therapeutic relationship is the means to provid-

TABLE 70–1. Current evidence-based treatments for borderline personality disorder

Treatment (supportive trials/total trials)	Description	Intensity	Allowed additional treatments	Length of intervention (months)	Length of follow-up (months)	Availability of training	Published treatment manual
Supported (RCT>1)							
DBT (13/13)	Behavioral therapy that teaches distress tolerance, emotional regulation, interpersonal effectiveness, and mindfulness	1x/week individual, 2x/week group; 1x/week group consultation for therapists	Medications (no protocol)	12	12	Yes	Yes
MBT (2/2)	Psychoanalytical/cognitive treatment that teaches skill of thinking about oneself and others in terms of meaningful intentional states	1x/week individual therapy, 2x/week group expressive therapy; 1x/week group consultation for therapists	Medications (APA protocol)	18	96	Yes	Yes

TABLE 70–1. Current evidence-based treatments for borderline personality disorder *(continued)*

Treatment (supportive trials/total trials)	Description	Intensity	Allowed additional treatments	Length of intervention (months)	Length of follow-up (months)	Availability of training	Published treatment manual
Supported (RCT>1) *(continued)*							
TFP (2/3)	Psychoanalytically based therapy that promotes integrated thinking about self and others through use of interpretation of transference	2x/week individual therapy; weekly supervision	Medications (no protocol)	12	No	Yes	Yes
STEPPS (2/2)	Education and skills-based intervention that educates about BPD and teaches emotional regulation and self-care skills	1x/week group; no weekly consultation	Individual therapy, medications (no protocol)	5	12	Yes	Yes

TABLE 70–1. Current evidence-based treatments for borderline personality disorder *(continued)*

Treatment (supportive trials/total trials)	Description	Intensity	Allowed additional treatments	Length of intervention (months)	Length of follow-up (months)	Availability of training	Published treatment manual
Promising (RCT=1)							
GPM (1/1)	Individual case management that addresses interpersonal/situational stressors and promotes accountability	1x/week individual; 1x/week supervision	Any, medications (APA protocol)	12	24	Yes	Yes
SFT (1/1)	CBT that teaches patient to change negative thinking and beliefs about self and others using CBT and experiential interventions	2x/week individual; 1x/week supervision	Medications (APA protocol)	36	No	Yes	Yes
CBT (1/1)	Therapy that teaches skills to change dysfunctional thoughts and behaviors	1x/1–2 weeks individual; as-needed consultation	Any, besides inpatient or specialized treatment	12	12	No	No

TABLE 70–1. Current evidence-based treatments for borderline personality disorder *(continued)*

Treatment (supportive trials/total trials)	Description	Intensity	Allowed additional treatments	Length of intervention (months)	Length of follow-up (months)	Availability of training	Published treatment manual
Promising (RCT=1) ***(continued)***							
CAT (1/1)	Therapy that integrates cognitive-behavioral and psychoanalytic concepts to promote awareness of interpersonal patterns and of problematic behaviors and their precipitants	1x/week individual; as-needed consultation	None	6	18	Yes	Yes

Note. APA=American Psychiatric Association; BPD=borderline personality disorder; CAT=cognitive analytic therapy (Chanen et al. 2008). CBT=cognitive-behavioral therapy; DBT=dialectical behavior therapy; GPM=general psychiatric management; MBT=mentalization-based treatment; RCT=randomized controlled trial; SFT=schema-focused psychotherapy; STEPPS=Systems Training for Emotional Predictability and Problem Solving; TFP=transference-focused psychotherapy.
For more extensive review (except of cognitive analytic therapy), see Stoffers et al. 2012.

ing therapy and is perceived as part of the therapy. The question of what aspects of DBT are responsible for effecting change has received some insightful study. In particular, therapeutic alliance was found to account for as much variance in symptomatic improvement in DBT as skills use (Turner 2000).

Mentalization-Based Treatment

Mentalization-based treatment (MBT), created by Bateman and Fonagy (1999, 2003, 2009), developed from Fonagy's pioneering observations about the obstacles that children at risk for BPD confront in their early attachment experiences (Fonagy et al. 2000). Specifically, Fonagy noted that these borderline children fail to develop a coherent or realistic sense of self without sensitive, timely, and accurate responses from their caretakers (Fonagy et al. 2000). Such caretaker responses provide a child with a language to identify feelings, an awareness of his or her effect on others, and a sense that actions (his or her own or others') are motivated. These capacities comprise *mentalization* (Choi-Kain and Gunderson 2008).

On the basis of these observations, the core psychopathology of BPD is hypothesized to be the inability to mentalize in situations of hyperactive attachment, and the core therapeutic task is to help patients learn to do this more stably. The effectiveness of this strategy was originally established in a study of 18 months of treatment within a specialized MBT partial hospital program, compared with treatment as usual (Bateman and Fonagy 1999). The MBT program consisted of individual therapy (1 hour/week), group therapy (2 hours/week), and expressive therapy (e.g., art studies). The focus was on here-and-now interventions, labeling of feeling states, and connection of actions to feelings or intentions by detailed chain analyses. Transference interpretations were eschewed. Moreover, after patients left the program, these gains continued to grow during a follow-up period of 8 years (Bateman and Fonagy 2009). More recently, MBT was tested as an outpatient package (without the milieu or expressive therapy components) and compared with structured clinical management (Bateman and Fonagy 2009); in this trial, MBT again proved superior, but the distinctions in outcome were less dramatic.

The effectiveness of MBT has been established using clinicians under Bateman's supervision at clinical sites outside London (Bales et al. 2012; Jorgensen et al. 2012). MBT is conceptually appealing. It bridges psychoanalytic and cognitive therapy approaches, and the target for change—that is, mentalization—may be central to all effective therapies (Allen et al. 2008).

Transference-Focused Psychotherapy

Kernberg's (1967) seminal contributions to understanding and treating patients with BPD have evolved into the publication of a manual for conducting transference-focused psychotherapy (TFP; Clarkin et al. 1999) that allows adherence and compliance to be measured (Clarkin et al. 2004). This is a major achievement because Kernberg's theoretical and clinical leadership helped impel the original therapeutic interest in patients with BPD and analytic therapies have traditionally defied operationalization.

TFP has adopted a hierarchy of goals (not unlike those described earlier for DBT) and recognizes the importance of feeling states (as in both DBT and MBT). Unlike either DBT or MBT, TFP has a much greater focus on identifying the distorted perceptions of relationships and

of the therapist and considering how these perceptions relate to past experience. In this regard, TFP has a closer association with traditional psychoanalytic therapies than does MBT.

TFP has been evaluated in three RCTs. In the first, TFP was compared with DBT and supportive psychotherapy (Clarkin et al. 2007). All three treatment conditions proved equally effective, but TFP appeared to be more effective on reflectiveness (an outcome variable akin to mentalizing). Given the better-established efficacy of DBT, this was a welcome validation of TFP's benefits. However, these results echo the earlier results of the Menninger Psychotherapy Research Project (Kernberg 1973); supportive therapy with less training and fewer scheduled hours did as well as TFP or DBT. TFP's effectiveness was confirmed in a second outpatient trial in which it was compared with treatment by community experts (Doering et al. 2010).

A third trial deserves extended comment both because its interpretation is unclear and because TFP was the comparator treatment to a notable theory-based manualized therapy for which training is available. In this trial, TFP was compared with schema-focused therapy (SFT) in a sample of 86 outpatients, randomly allocated to either treatment (Giesen-Bloo et al. 2006). The treatments lasted 3 years and were conducted by therapists supervised for adherence to the respective treatment model. The study authors reported superiority of SFT in terms of symptomatic outcomes and improvements in well-being. Validity of the conclusions of this RCT was called into question, however, by the supervisor of the TFP therapists who noted their poor adherence to TFP (Yeomans 2007).

SFT postulates that patients with BPD have disturbed cognitions ("core beliefs") that developed early in their lives, with maladaptive consequences that are self-perpetuating and are the targets for change. The specific maladaptive cognitive schemas proposed by Young et al. (2003) for BPD that are targets for change in SFT are abandonment and loss, unlovability, dependence, subjugation, lack of identification, mistrust, inadequate self-discipline, fear of losing emotional control, guilt and punishment, and emotional deprivation.

In addition to the comparison with TFP noted above, modified forms of SFT have been evaluated in two other RCTs, although comparison among these studies is limited by variations made in SFT and by design issues. Farrell et al. (2009) studied the effectiveness of a group therapy form of SFT versus treatment as usual. The intervention lasted 30 sessions. Results supported effectiveness of group SFT in terms of BPD symptomatology, psychiatric symptoms, and general functioning. Nadort et al. (2009) compared regular SFT with SFT augmented with phone availability of the therapist; no differences were found. SFT's value remains to be tested, versus treatment as usual, in shorter-term trials, and potentially in combination with its group therapy variant. As shown in Table 70–1, it remains within the group of EBTs that are "promising."

Systems Training for Emotional Predictability and Problem Solving

A treatment developed by Blum, St. John, and Pfohl, beginning in 1995, Systems Training for Emotional Predictability and Problem Solving (STEPPS), like DBT, describes BPD as a disorder of emotional and behavioral dysregulation, with self-destructive behaviors providing temporary relief of emotional distress. STEPPS

was designed to educate patients with BPD (primarily) as well as significant people in their immediate environment (e.g., friends, family, therapists) regarding constructive ways to manage distress, promote functional behaviors, and discourage ineffective ones. An accompanying booklet covers such topics as awareness of illness, emotional management skills training, and behavioral management skills training (e.g., communication, managing problems, healthy eating, sleep hygiene, leisure).

The standard version of this treatment has been tested in two RCTs (the third RCT used a modified version) conducted in two different settings, demonstrating that STEPPS can be successfully implemented in other settings and by therapists other than its developers. In the first RCT (Blum et al. 2008), 124 subjects with BPD were randomly assigned to STEPPS plus treatment as usual (TAU) or to TAU only. Subjects assigned to STEPPS+TAU experienced greater improvement in the BPD symptoms, as well as global functioning, but not in suicide attempts, self-harm, or hospitalizations. During the 1-year follow-up, fewer STEPPS+TAU subjects had emergency department visits. In the second RCT (Bos et al. 2010), conducted in the Netherlands, 79 patients with BPD were randomly assigned to receive STEPPS +TAU or TAU only. STEPPS was associated with a greater reduction of BPD and other symptoms, as well as larger improvement in quality of life. In the third RCT, STEPPS was modified for adolescents (i.e., 17 sessions plus two booster sessions; more age-relevant content) and tested as Emotional Regulation Group (ERG) training (Schuppert et al. 2009) in which 43 adolescents (ages 14–19 years) were randomly assigned to receive either ERG+TAU (n=23) or TAU alone (n=20). Both groups showed similar levels of improvement in BPD symptoms; participants in ERG+TAU reported more sense of internal control over mood. The study was limited by a high dropout rate, particularly in the ERG +TAU group (39% in the ERG+TAU group vs. 15% in the TAU group).

Generalist Approaches: Clinical Management and Supportive Psychotherapy

In the earliest phase of research testing specialized psychotherapeutic approaches for BPD in RCTs, investigators tested their treatments against treatment as usual conditions, which were uncontrolled, inconsistent, and unstructured (Bateman and Fonagy 1999; Linehan et al. 1991). Although these trials contributed significantly to the literature in providing evidence that patients with BPD could respond positively to specialized treatments, the comparative bar for demonstrating effectiveness and superiority was set low. Most subsequent trials tested other specialized psychotherapeutic approaches at a higher standard of comparison, incorporating either good clinical management or supportive therapies as their comparison condition (Bateman and Fonagy 2009; Clarkin et al. 2004, 2007; McMain et al. 2009; Jorgensen et al. 2012). Although the intention in this effort was to show that the specialized approaches provided therapeutic benefits driven by mechanisms other than basic informed care, structure, consistent attention, and accessible support, the result proved that these more labor-intensive treatments yielded improvements comparable to, and only in some cases marginally better than, either good clinical management or supportive therapy.

Two large treatment trials, one using DBT (N=180; McMain et al. 2009) and one using MBT (N=134; Bateman and Fonagy 2009), tested specialized approaches to structured generalist treatment informed by best practice guidelines for BPD combined with supportive and problem-solving interventions. In both trials, the generalist approaches—Structured Clinical Management for BPD and general psychiatric management (Gunderson and Links 2014)—did as well as DBT and MBT in reducing symptoms and improving functioning. Another MBT study (Jorgensen et al. 2012) and one study of TFP versus DBT (Clarkin et al. 2007) also incorporated an arm of supportive therapy. The supportive therapy arm of the TFP/DBT trial was notably psychoanalytically oriented. In both studies, the frequency of the supportive therapy was less intensive than in the specialized psychotherapeutic comparison treatments, yet supportive therapy yielded significant and comparable improvements in subjects. Altogether, these data on structured clinical management and supportive therapy in the treatment of BPD suggest that elements of informed care, structured treatment, available support, and practical problem solving, packaged in lower-intensity care with fewer clinical resources, may provide the most practical and generalizable EBT for BPD.

Multimodal Treatments

It is notable that both DBT and MBT combine group and individual therapies and that general psychiatric management endorses split treatments. Even without empirical support, there are clinical and conceptual reasons to conclude that split treatments have advantages over the traditional reliance on individual therapy alone. First, there is the advantage that different modalities offer different effects (as discussed in the following subsections), and combining them automatically broadens the range of expectable outcome benefits. Second, the presence of a second treater provides automatic coverage and a colleague to share problems with, which helps diminish the burden and liability for treaters. Third, we believe that split treatments diminish noncompliance, dropping out, and probably self-harm; this is because split treatments provide the patient with BPD who is angry at a treater with another treater to complain to without having to communicate by defiance or leaving. This offers a built-in "holding environment." The reasons that split treatments have still not become the standard for treating patients with BPD are related to feasibility (a second treater may not always or easily be available) and to fears that these patients will "split" the treaters into incompatible and hostile stances and then take advantage of the situation. It seems apparent now that when treaters communicate and respect each other, splits do not occur.

Structure

A primary clinician needs to be involved, and there also needs to be open and accessible communication among treaters. The primary clinician is responsible for overseeing safety, assessing progress, and making decisions about changes in the treatment, and therefore is essentially the case manager (see first principle in the earlier section "General Principles of Effective Therapies"). This role especially needs to be clarified when the psychiatrist does only medication management but someone else is responsible for safety. Respect for and communication between treaters is essential. Although patients may object, it should be a necessary pre-

condition that the treaters have the right and expectation that they will communicate as they deem necessary.

Group Therapies

The overall role of group therapies is easily underestimated. This is in part because patients with BPD usually object to this modality—for the very reasons that groups are so valuable. Namely, groups require sharing of attention and self-disclosures, require learning to tolerate feelings from others, and are the best vehicle for learning how one affects others, for learning empathy, and for identifying how and why others affect oneself—that is, they are the best way to learn mentalization skills. Groups are the ideal therapy to add to case management/individual therapy because not only are the effects complementary, but a group is the most cost-beneficial modality. Outpatient clinics that serve patients with BPD should make participation in a group therapy mandatory. There are a range of types of group therapy that help patients with BPD (see Gunderson and Links 2008), but the general principle is that more structured and situation-focused groups are less stressful, whereas less structured groups are more feeling and interpersonally oriented.

Family Interventions

Some families are so dysfunctional or hostile to psychiatric help that the best treaters can do is help the offspring with BPD become reconciled to this situation. In most cases, however, it is possible and highly rewarding to involve the families. Even when parents have had a significant role in their offspring's environmental adversity, they will generally be burdened by their child's behavioral problems (Goodman et al. 2011) and welcome some help. The simplest, most acceptable, and most essential type of family intervention is psychoeducation. All patients and families need to become informed consumers. This means knowing the basics about the origins, course, and treatments for BPD. This establishes reasonable expectations and diminishes interfamily blaming. The next level of family intervention involves advice, coaching, and problem solving. Most families are aware that what they have been doing does not work, so they are often glad to follow advice. More complicated and stressful interventions are those that ask the patients and families to address their grievances—or other feelings—toward each other. This type of intervention should be reserved for those families who are able to listen to one another's criticism without becoming too upset or having to leave.

Pharmacotherapy

Medications have an adjunctive role in the treatment of BPD. The U.S. Food and Drug Administration has yet to approve any medication for BPD. Although many types of medication can be helpful, the benefits are neither dramatic nor consistent. Their role often gets misunderstood when physicians, who otherwise feel quite helpless about being helpful, prescribe medications without clarifying that the expectations for change should be modest. As important as that message is, it is also essential to communicate that the patient needs to be an active partner in evaluating benefits. This message conveys the need for the patient to assume a responsible role, but also clarifies that assessing progress is an essential aspect of whether medications will be continued or changed. Failure to convey this message encourages both passivity and polypharmacy. While enjoining the patient to be active in evaluating medication effects, prescribers need to be aware that

they cannot expect a patient with BPD to be a good judge of benefits. These patients are likely to be dissatisfied with medications that are inhibitory (Cowdry and Gardner 1988).

Only about 30 controlled trials of medications in patients with BPD have been reported. The collective strength of this body of research is further limited by the fact that the studies had different comparison groups, outcome measures, and lengths of follow-up. Early studies looked at phenothiazines and tricyclic antidepressants. They generally found modest effects, although the antipsychotics had more effects on depression than did the antidepressants. These results have been confirmed in a second generation of studies that used selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics. In recent years more attention has been given to mood stabilizers, which appear to have broader effects than either the antipsychotics or the antidepressants (Table 70–2), but still we emphasize that the effects of mood stabilizers are neither dramatic nor consistent. The official American Psychiatric Association guideline for treatment of BPD from 2001 (Oldham et al. 2001) needs to be revised to incorporate the evidence that mood stabilizers have an enlarged role and that the benefits from SSRIs appear to be less than had been thought. A number of reviews of the medication literature have been published in recent years (Bellino et al. 2008; Ingenhoven and Duivenvoorden 2011; Mercer et al. 2009; National Institute of Clinical Excellence 2009; Silk 2011; Stoffers et al. 2010). Although most reviews favored the overall utility, albeit modest, of medications, several had more negative conclusions. Specifically, the review by the National Institute of Clinical Excellence (2009) concluded that there was not sufficient evidence for any medication regimen to be endorsed, and Bellino et al. (2008), after conceding that pharmacological therapy of BPD has modest value, also noted that the research evidence is inadequate.

Not all BPD symptoms respond to pharmacological interventions. Interpersonal instability and affective dysregulation may respond to antipsychotic medication and mood stabilizers, whereas impulsive-behavioral dyscontrol symptoms are apt to respond to antipsychotics, mood stabilizers, and perhaps to SSRIs. However, avoidance of abandonment, chronic feelings of abandonment, identity disturbance, and dissociation do not seem to respond to any specific medications (Stoffers et al. 2010), thus highlighting the central role of psychosocial interventions in addressing these symptoms. Effects of medications on global functioning and adaptation have been tested in very few trials, with only small changes reported (Bellino et al. 2008; Ingenhoven and Duivenvoorden 2011).

The issue of medication use is increasingly complicated by the growing understanding of the relationship of BPD to its co-occurring disorders. Most notably, there is evidence that BPD affects MDD's course very negatively (Grilo et al. 2010; Gunderson et al. 2008; Skodol et al. 2011) and that antidepressants have only modest effects on MDD when it co-occurs with BPD (Mercer et al. 2009). Because remission of BPD greatly affects MDD's course and remissions (Gunderson et al. 2004), treatment of BPD should assume priority when these disorders co-occur. BPD's relationship to bipolar disorder is notable insofar as neither disorder greatly influences the course of the other, although BPD does increase the risk of a new onset of bipolar disorder

TABLE 70–2. Symptom targets and medication types

Medication type	Symptom targets					
	Mood instability	Depression	Anxiety	Anger	Impulsivity	Cognition/ perception
Selective serotonin reuptake inhibitors	?	+	?	?/+	+	–
Tricyclic antidepressants	–	–	–	+/?	?	–
Mood stabilizers	+	?/+	?	++	++	–
Antipsychotics	+	?	+	+	+	++
Anxiolytics	?	–	?	–	–	?

Note. ++=very helpful; +=helpful; ?=uncertain; –=negative.
Source. Adapted from Mercer et al. 2009; Silk 2011; Stoffers et al. 2010.

(Gunderson et al. 2004). Therefore, although mood stabilizers may benefit BPD, they do not have powerful effects on either disorder when they co-occur. As a result, in addition to using mood stabilizers, it remains essential that the BPD be given equal or greater treatment priority to bipolar disorder.

The effects of co-occurring substance use disorders (SUDs) on BPD are important given the high rates of co-occurrence. SUDs are known to have very negative effects on BPD's course (Zanarini et al. 2004). When a patient is actively abusing to the extent that the SUD interferes with therapy attendance, concentration, and therapeutic effects of prescribed medication, SUD should become the highest treatment priority—making treatment for BPD contingent on the patient's having established a period of sustained abstinence. This does not mean that SUD relapses or intermittent abuse is inconsistent with treating BPD. BPD also has a very negative impact on SUDs, and its remission will certainly diminish substance use. Because SUD and BPD escalate effects of each other, effective treatment should address both conditions simultaneously, helping the patient to abstain from substances and develop more effective ways to manage those difficulties associated with both BPD and substance use, emotional dysregulation, impulsivity, and interpersonal dysfunction.

Levels of Care

In general, the least restrictive level of care necessary is always the best. The best level is the one that provides the structure and support needed for the patient with BPD, but not so much as to divert the patient's attention from his or her problems when he or she has less structure and support—that is, when the patient is having problems with coping, assuming responsibilities, and tolerating aloneness, rejections, or criticisms.

Treatment on any level of care will always be more effective when patients and treaters have a common understanding of the etiology, expectable course, and the "General Principles of Effective Therapies" presented earlier in this chapter. Psychoeducation is always an important alliance-building exercise.

Summarizing statements about each level of care based on our personal experience are provided in Table 70–3. In the review about each level that follows, we emphasize empirical evidence where it is available.

Hospital Care

There are no RCTs supporting treatment of BPD patients in inpatient settings versus treatment at other levels of care. Of note, inpatient DBT was evaluated using pre-post design studies that confirm its effectiveness in reducing BPD symptoms, both at discharge and at 1- to 21-month follow-up (for a review, see Bloom et al. 2012). Because pre-post studies can be expected to show positive results, given the natural course of BPD, these studies cannot show whether DBT adds value to usual inpatient treatment.

Because of the limited lengths of hospital stays, only short-term interventions with a focus on symptom relief are feasible (see Table 70–3). Hospitals are the most widely available resource for patients with BPD and, although invaluable for safety and assessment, they can be poorly used for these patients. The most common mistakes are overuse for deliberate self-harm; failure to make or disclose the BPD diagnosis and to offer psychoeducation; overemphasis on medication; and discharge without aftercare.

Staff who work in hospital units should be trained in assessment of the danger-

TABLE 70–3. Characteristics of level of care

Level of care	Usual LOS	Clinical tasks	Central modalities	Level of empirical support
Hospital 24 hours/day; 7 days/week	1–2 weeks	Assure safety, stabilize emotions, change treatments, address situational stressors	Case management, medications, psychoeducation	Moderate
Partial (day) hospital 10–20 hours/week	1–6 weeks	Control impulses, build alliance, stabilize/assist community living	Case management, groups (cognitive-behavioral, self-assessment), psychoeducation	Weak
Intensive outpatient 4–10 hours/week	3–12 months	Control emotions, build assertiveness, improve listening and self-disclosure	Case management, groups (skills, interpersonal), individual psychotherapy	Strong
Outpatient 1–3 hours/week	Indefinite	Improve introspection and sense of agency, generalize skills	Case management, individual psychotherapy, groups (interpersonal, mentalization)	Strong

Note. The lengths of stay identified here are estimates of what is normative in the United States at this time. This table is built from the authors' clinical impressions of what should be standards of care. They are not scientifically established or official.
LOS=length of stay.

ousness of suicide and deliberate self-harm and in their management. Other important staff interventions include validation of patients' subjective distress, attention to situational stressors, and the ability to set limits. Limit setting introduces the issue of accountability and diminishes the potential for destructive effects on others, secondary gain assessment, and management.

Partial (Day) Hospital

Effectiveness of an 18-week day hospital program was supported in one RCT in which a sample of patients with mixed personality disorders assigned to the day program was compared to a group of patients assigned to outpatient psychotherapy. Both treatments demonstrated similar effectiveness postdischarge (Arnevik et al. 2009), but the outpatient therapy condition had superior efficacy at 36-month follow-up (Gullestad et al. 2012). A pre-post design study of an MBT-based partial program showed significant reduction in suicide attempts, self-harm, and use of costly health care resources (Bales et al. 2012). In another pre-post design study in 47 female patients with BPD participating in a partial program, Yen et al. (2009) reported decreases in depression, hopelessness, anger expression, dissociation, and general psychopathology at 3 months postdischarge. A pre-post design study of a sample of patients with mixed personality disorders who completed an analytically oriented day treatment reported modest improvements in symptomatic and functional improvements that were maintained at follow-up (Wilberg et al. 1998). As with the research on hospital care, research projects lacking a comparator treatment leave it unclear to what extent the observed improvements are the natural course of the disorder.

Because partial hospital programs combine significant structured support with concurrent community involvement, they are well suited for many patients with BPD. In this respect, their relative unavailability is unfortunate. It is a good setting to address maladaptive behaviors (impulsivity, anger) and to establish a contractual alliance (i.e., agreed-upon goals and roles). Staff who work in partial hospital settings require crisis management skills, the ability to recognize and respond to calls for help with concerned attention (without overreacting), and the ability to teach impulse-control strategies. Among the most common mistakes at this level of care are insufficient attention to social situations and stressors, failure to collaboratively establish feasible goals, and failure to develop a viable aftercare plan. Still, this level of care is represented in the split individual plus group treatments of DBT and MBT (for a meta-analytic review, see Stoffers et al. 2012).

Intensive Outpatient Care

Like partial hospital care, intensive outpatient care is another level of care that is particularly well suited for many patients with BPD but is not widely available. Its level of intensity and duration allow actual therapeutic processes to evolve and observable changes to occur. As in partial hospital care, group therapies are the central interventions; however, in intensive outpatient care, more process-oriented groups, such as those using interpersonal or mentalization therapies, are valuable. Initiation of individual therapy can gain support from the concurrent case management and other modalities that facilitate establishing an alliance.

Team collaboration and communication, as noted in structuring multimodal treatments (see the earlier section "Multimodal Treatments"), is essential for cli-

nicians working within this intensive outpatient care. Splitting of treaters into different "camps" is usually an unnecessary artifact of poor staff communication. All team members need to be involved with the patients (the third principle in the earlier section "General Principles of Effective Therapies") and to take initiative in addressing absences, devaluation, and safety concerns.

Common mistakes within intensive outpatient care include insufficient assessment of a patient's involvement such that pseudotherapies or secondary gain issues go unaddressed. This occurs when insufficient attention is paid to monitoring change.

Outpatient Care

The relative strength of empirical support for outpatient care has to do with the high number of RCTs (20 in the review by Stoffers et al. 2012) and their consistently positive results, as well as their methodological strength. This support is particularly important because most patients with BPD receive most of their treatment as outpatient care.

Within outpatient therapies, it is essential that patients develop more interest in their internal states and how these relate to their world. They need to see themselves as agents in determining their fates. For those who have had skills training within more intensive levels of care, the question of whether to apply those skills becomes an essential issue. Central modalities include case management (as usual) and individual psychotherapy, which is often most important; group therapies (interpersonal, mentalization) and family interventions are significant and sometimes essential. Although the availability of outpatient treatment is high, adequately trained and interested clinicians are in limited supply. Staff who do outpatient therapies need to be comfortable with anger and their own personal limits, and to have sustained countertransference awareness. In the absence of other clinicians, utilization of supports and consultations requires willingness and initiative by outpatient therapists. Although countertransference enactments are most apt to occur at this level of care, they remain quite rare. A more common problem is that the focus on the patient's feelings and psychology occur at the expense of adequate attention to his or her ongoing social disabilities (e.g., work).

Conclusion

The growing research base for treatment of BPD has definitely demonstrated that informed treatments can expedite improvement in this disorder. Studies have documented the dramatic effectiveness of various psychotherapies, the inconsistent benefits from pharmacotherapies, the need for better social rehabilitative therapies for BPD, and the essential value of different levels of care and of sociotherapies (e.g., group, family). Because a second generation of research has used more structured comparator treatments, the magnitude of the differences between treatment arms is much reduced. It is now evident that the comparator treatments, which generally involve support and case management, can offer a good treatment for most BPD patients. These advances in knowledge about psychotherapies still have not been extended into the general standards of health care. Such good case management practices now need to be incorporated into basic training for all psychiatrists and psychologists who take on the responsibility of treating patients with BPD.

In future editions of this book, chapters on BPD are unlikely to give the same

level of emphasis to individual psychotherapies as in the earlier editions. The reasons for this are multiple: First, patients can and usually do get significantly better without individual psychotherapies. Thus, the basic care of these patients involves a variety of other interventions that can effectively facilitate improvement. These shorter-term case management–level interventions are what clinicians need to know. Second, well-informed case management is sufficient for most patients with BPD to improve significantly. This has now been repeatedly documented when such case management is compared with the validated EBTs (Bateman and Fonagy 2009; Chanen et al. 2008; Clarkin et al. 2007; McMain et al. 2009). Third, stable ongoing individual psychotherapies are rarely feasible: extensive therapist training, the heavy financial burden, and the limits of patient motivation for such therapies greatly limit their use.

Some major gaps remain in this otherwise generally positive review of current treatment practices. The first of these involves the persisting lack of any medication that has consistent or strong effectiveness. The growing knowledge bases about both BPD's neurobiological substrates and the aberrations of neurohormones offer promising arenas for development of a BPD-specific pharmacotherapy. A second major gap concerns the overall ineffectiveness of existing treatments to greatly improve the social adaptation of patients with BPD. Evidence that the social adaptations of these patients remain persistently impaired even after the symptoms remit indicates that treatments need to address this other major sphere of outcome. The public health costs of such disability far exceed the costs of treatment (Soeteman et al. 2008; van Asselt et al. 2007). Rehabilitation interventions now need to be given more emphasis.

Currently, clinicians treating patients with BPD should begin with the recognition that although long-term treatment may sometimes be necessary, time-limited and focused interventions are the usual building blocks for recovery. Our impression is that the overall care of patients with BPD is improving. There appear to be fewer instances of the inappropriate applications of psychoanalysis and of severe boundary violations. Regardless of whether this is true, in this new era, the treatment of BPD can be undertaken with better-informed and justifiable optimism and with more appreciation that effective treatment relies on wise utilization of diverse modalities.

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CHAPTER 71

Histrionic Personality Disorder

Glen O. Gabbard, M.D.

No body of treatment research exists for histrionic personality disorder (HPD). Although two meta-analyses of psychotherapeutic treatments for personality disorders (Leichsenring and Leibing 2003; Perry et al. 1999) suggest that these conditions respond to both psychodynamic therapy and cognitive-behavioral therapy, none of the included studies focused specifically on HPD. Most of the literature on this diagnostic entity has been written from a psychodynamic/psychoanalytic point of view. Recently, contributions from cognitive therapy have appeared. Both approaches are summarized in this chapter, and the discerning reader will note considerable overlap between the two therapeutic strategies. The lack of rigorously designed treatment trials on HPD requires therapists to rely on accumulated clinical wisdom regarding the treatment of these patients. No medications have been systematically studied, and clinicians do not think about medications as particularly useful for this group of patients. Hence, psychotherapy must be considered the cornerstone of treatment.

HPD is the latest incarnation in the psychoanalytic tradition of hysterical character neurosis or hysterical personality (see Box 71–1 for the DSM-5 diagnostic criteria for HPD [American Psychiatric Association 2013]). As a diagnostic entity, HPD encompasses a spectrum ranging from a higher-level or neurotically organized patient, comparable with the classical hysterical character neurosis, to a more primitively organized variant whose clinical features have considerable overlap with borderline personality disorder.

Indeed, Blagov and Westen (2008) asked a group of 1,201 experienced clinicians to describe a random patient with personality pathology using rigorous psy-

chometrics, including the Shedler-Westen Assessment Procedure–II (SWAP-II), a Q-sort that captures personality and its pathology in adults. Using DSM-IV–based measures, they identified patients whose personality functioning met HPD criteria and found that the most descriptive and most distinctive features of the patients included some features of HPD but also many features of borderline personality disorder.

A study of 2,289 patients treated for personality disorders in psychotherapeutic day hospitals in Norway (Bakkevig and Karterud 2010) found a very low prevalence of HPD (0.4%). Most striking was the high comorbidity of HPD, particularly with borderline, narcissistic, and dependent personality disorders. The authors concluded that the HPD category has poor construct validity. This overlap of HPD with other personality disorders, along with the paucity of research, was a major reason that the DSM-5 Personality and Personality Disorders Work Group recommended the deletion of this diagnosis from the official diagnostic manual.

Box 71–1. DSM-5 Diagnostic Criteria for Histrionic Personality Disorder

301.50 (F60.4)

A pervasive pattern of excessive emotionality and attention seeking, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Is uncomfortable in situations in which he or she is not the center of attention.
2. Interaction with others is often characterized by inappropriate sexually seductive or provocative behavior.
3. Displays rapidly shifting and shallow expression of emotions.
4. Consistently uses physical appearance to draw attention to self.
5. Has a style of speech that is excessively impressionistic and lacking in detail.
6. Shows self-dramatization, theatricality, and exaggerated expression of emotion.
7. Is suggestible (i.e., easily influenced by others or circumstances).
8. Considers relationships to be more intimate than they actually are.

Despite the concern about the validity of the diagnosis, there is little doubt that individuals who receive this diagnosis live with a good deal of suffering and emotional pain. Skilled clinicians continue to find the diagnosis useful in identifying a cluster of features that provide a conceptual framework that is useful to psychotherapists. Moreover, some research suggests that the characteristics found in these patients are particularly fixed and may not decline with maturity. Although many personality disorders show declines in symptomatology over time, one study of 1,477 patients (Gutiérrez et al. 2012) showed that patients with HPD do not show linear reductions in the clinical features over the course of life. Moreover, they may resort to substance abuse to deal with their distress. In an epidemiological study of over 40,000 individuals (Trull et al. 2010), HPD had the highest rate of comorbidity with lifetime drug dependence (29.72%) of all personality disorders. Persons with HPD clearly are in need of treatment, and clinicians

must carefully assess the level of personality functioning so that therapy can be tailored to the individual patient.

Overt interpersonal characteristics may not be extremely useful in understanding the underlying psychodynamic organization of patients with HPD. Horowitz (1997, 2001), for example, has noted that patients who exhibit an interpersonal style characteristic of HPD may be psychiatrically healthy, neurotic, narcissistic, or borderline in terms of the coherence of their identity and the continuity of their regard for significant others. Overt behavior characteristics, such as attention seeking, self-dramatization, disturbed sexual functioning, dependency, helplessness, and labile and shallow affect, link patients at the higher and lower levels of the spectrum on the surface. The psychotherapist must make fine distinctions between neurotically organized individuals, who can be treated with psychoanalysis or a highly exploratory psychotherapy, and individuals with more limitations, who may require much more of a supportive-expressive approach.

Table 71–1 summarizes the differences between patients with the higher-level (neurotic or hysterical) variant and those with the more disturbed (primitive) variant of HPD. These distinguishing characteristics may provide a psychodynamic therapist with the capacity to tailor the treatment in a more exploratory or supportive direction, based on the strengths and weaknesses of the patient (Gabbard 2014).

The emotionality of the more primitive variant is much more florid and dramatic than that of its higher-level counterpart, for which affect is often restrained and circumscribed unless specific issues are involved, such as romantic relationships. Although there is a tradition of linking hysterical patients to sexually exhibitionistic behavior, this feature may be confined to subtle ways of moving or looking or interacting, whereas there is a much more demanding and overt quality to the exhibitionism of patients at the lower end of the spectrum. This "over-the-top" behavior of these patients may be related to more general problems of impulse control when under stress or intense affective pressure. Similarly, seductiveness among such patients is sometimes so aggressive and inappropriate as to actually distance the other party. The patients with the more primitive variant also tend to be more helpless and aimless and to make more overt appeals for caretaking from others.

Neurotically organized (hysterical) patients are capable of mature, triangular interpersonal relationships, such that they often find themselves falling in love with unavailable partners for whom a romantic rival is very much in the picture. This repetitive pattern of object relations leads to a great deal of anguish. By contrast, the primitive clinging quality of patients on the lower end of the spectrum has a much more dyadic feel, as though there is no awareness of anyone but the object of affection. Similarly, separations are much better tolerated by neurotically organized patients, and their harsh superego leads them to feel tormented by moral concerns. Patients who are more primitively organized have a more lax superego that is at times absent and at other times self-critical. Finally, the type of sexualized transferences that develop are strikingly different between patients at the two extremes of the continuum. Those on the more primitive end are likely to develop *erotized* transferences that involve intense ego-syntonic demands for sexual gratification from the therapist. Neurotically organized patients are more likely to have *erotic* trans-

TABLE 71–1. Differentiation of neurotic and primitive variants of histrionic personality disorder

Neurotic (hysterical) variant	Primitive variant
Restrained and circumscribed emotionality	Florid and generalized emotionality
Sexualized exhibitionism and need to be loved	Greedy exhibitionism with a demanding quality that is "cold" and less engaging
Good impulse control	May become impulsive under stress
Subtly appealing seductiveness	Crude, inappropriate, and distancing seductiveness
Ambition and competitiveness	Aimlessness and helplessness
Mature, triangular interpersonal relationships	Primitive, dyadic interpersonal relationships characterized by clinging, masochism, and paranoia
Separations from love objects can be tolerated	Overwhelming separation anxiety when abandoned by love objects
Strict superego and some obsessional defenses	Lax superego with proneness to rely on primitive defenses, such as splitting and idealization, when under stress
Sexualized transference wishes develop gradually and are viewed as unrealistic	Intense sexualized transference wishes develop rapidly and are viewed as realistic expectations

Source. Adapted from Gabbard GO: *Psychodynamic Psychiatry in Clinical Practice,* 4th Edition. Washington, DC, American Psychiatric Publishing, 2005, p. 545. Used with permission.

ference wishes that are viewed as ego-dystonic and shameful. The latter group does not regard sexual contact with the therapist as a realistic possibility.

These distinctions are highly relevant to a psychoanalyst or psychodynamic therapist because they inform the therapist's strategy along the expressive-supportive continuum (Gabbard 2010). However, the cognitive therapist is less concerned about these distinctions based on psychodynamic constructs and does not focus as much on support versus exploration.

Hysterical personality was traditionally associated with the female gender, because it implied a connection with the classical notion of *hysteria* as "wandering uterus." The way that the term is used in common parlance often reflects caricatures of exaggerated femininity. Nevertheless, histrionic personality types are regularly found among males, and clinicians must work against cultural sex-role stereotypes when making the diagnosis. Mitchell (2000) pointed out that males with hysteria have become marginalized in psychoanalytic theory and practice because the symptoms of hysteria have been feminized over time. The basic symptoms, however, including seductiveness, sexual jealousy, longing for ideal love, emotional shallowness, and sexualization, occur in both genders.

Individual Psychodynamic Psychotherapy and Psychoanalysis

Psychodynamic Themes

A psychodynamic approach to HPD involves several different domains that serve as targets of the therapy. The presence of internal conflict leads to characteristic defensive patterns that must be addressed. The internal object relations of the patient often are repeated in interpersonal relationships again and again and may create difficulties in the patient's life. The patient's ongoing sense of self may require attention as well. Finally, the global impressionistic cognitive style so typical of patients with this diagnosis may work against the consideration of detail necessary for changes from in-depth psychotherapy, so attention is also needed on this domain.

At the beginning of the treatment, a careful psychodynamic assessment needs to be made to assess the patient's position in the spectrum of neurotic (hysterical) versus primitive features, as described earlier (see Table 71–1). The more the patient fits the higher-level profile, the more the psychotherapist can take an interpretive and exploratory approach. Those patients with strong motivation to understand themselves in depth may wish to engage in psychoanalysis four times weekly. Others may be content with face-to-face therapy once or twice weekly. Patients with a predominance of primitive features may require more support and structure. In addition, a variety of psychodynamic themes that are common among patients residing on the histrionic-to-hysterical continuum must be evaluated and understood in an ongoing way so that they can be brought to the patient's attention in the course of psychotherapy.

Many of the psychodynamic issues are linked to developmental models of pathogenesis. These models may or may not apply to a particular patient and must be used as working hypotheses that may need to be discarded as more clinical data emerge in the treatment. In the case of the histrionic female patient, the lack of maternal nurturance leads her to turn to her father for the gratification of dependency needs (Blacker and Tupin 1977; Hollender 1971; MacKinnon et al. 2006). She soon learns that flirtatiousness and dramatic, exhibitionistic displays of emotion are required to gain her father's attention. As she matures, she learns that she must repress her genital sexuality to remain "Daddy's little girl." When the little girl grows up, the primitive neediness characteristic of all her sexual relations may be termed the *breast-penis equation.* She often engages in promiscuous sexual behavior that is ultimately unsatisfying because the male penis only serves as a substitute for the maternal nurturance she unconsciously longs for.

The goal of these patients is often to be the object of desire to others (Bollas 2000). In the case of the little girl, she may feel she has lost out to her mother and will do whatever she can to become her father's object of desire. Often, this may lead to a false self-adaptation in which she suspends her true nature to try to become what others want. Many histrionic women approach men by trying to become what they think men would most want them to be, and the men end up disappointed because they feel they have been deceived by these women's inauthentic presentations of themselves.

Bollas (2000) noted that hysterical persons tend to create a life narrative in which they are the erotic objects of some-

one else. They spend much of their lives trying to find an "object in waiting" (p. 12) that will recast them as that individual's object of desire. The phenomenon of multiple romantic partners typical of patients with HPD often unfolds in a fixed pattern: for females with HPD, the chosen romantic man will never be the right one and is therefore expendable. In this way, these women save themselves for the father. As little girls, they often idealized their father, perhaps as the only man worth having. This intense attachment led to rivalrous feelings toward the mother and active wishes to replace her. In the course of therapy or analysis, many patients with HPD recall fantasies of this nature. If they perceive that their brothers are granted special status with their fathers by virtue of their male gender, the females also may develop deep resentment and may become highly competitive with men.

Although anorgasmia has classically been associated with hysteria, sexual symptomatology actually is much more varied in patients with hysterical or histrionic personality disorder. Some may have relatively asymptomatic sexual functioning but are cut off from any authentic inner experience of love or intimacy during sexual relations. Sexual body parts may be exhibited through provocative ways of dressing, even though there is little erotic arousal associated with the provocative behavior. In fact, a common occurrence in female hysterical and histrionic patients is surprise when others respond to them as though they are seductive or sexually provocative. In other words, there is a dissociation between the overtly sexualized behavior unconsciously designed to attract attention and the empathic attunement to how it will affect others.

For women with HPD, all sexuality may be tinged with incestuous meanings because of the oedipal attachment to the father. These women also may choose inappropriate partners as a further defense against giving up oedipal longings. These dynamics are often covert, however, and may become clear only after a careful evaluation. Although some women with the neurotic variant of HPD may have overt, conscious attachments to their fathers, others will have repressed this dimension of development. Their conscious experience of their father may be tinged with anger as a defense against their underlying longing. Similarly, they may be unaware of their rivalrous feelings toward their mother, whom they consciously love. Evidence of hysterical dynamics in the female patient may come instead from persistent patterns of triangular relationships, such as falling in love with married men, or from slowly emerging developments in the transference, such as feeling intense rivalry with other female patients. Whether or not the dynamics are repressed may depend on the father's response to his daughter's oedipal longings. If he views such feelings as unacceptable, he will convey this attitude to his daughter, who will then feel that she must repress them.

The exaggerated theatrical behavior typical of these patients often relates to a core experience of early childhood that involved not being recognized. In other words, parents who were too self-absorbed, too depressed, or too resentful of their child's developmental needs may have tuned out the child and not recognized the child's internal affective experience. In this regard, caregivers may not have served the necessary containing function to help the child process and metabolize overwhelming and frightening affect states. As Riesenberg-Malcolm (1996) stressed, the hyperbole or exaggeration may be an effort by patients to distance themselves from what is going

on internally while also making others take notice of unrecognized emotions. A Dutch study (Lobbestael et al. 2010) evaluated a sample of 409 patients to investigate the relationship between early abuse/neglect and personality disorders. Emotional neglect was clearly linked to HPD. Hence, there is very likely a developmental issue at play when the patient appears to be demanding attention—a desperate effort to elicit a response that was lacking in childhood.

Gender Differences

Many of the developmental dynamics that apply to female patients apply in a similar way to male patients. Whereas a histrionic female is often a "daddy's girl," a histrionic male has often been a "mama's boy." Histrionic males may react to separation-individuation themes in their childhood by erotizing the absent object (Bollas 2000). As soon as the maternal object is away, they imagine their mothers with another man who is preferred over them. Hence, many males with hysteria of the Don Juan variety are tormented by a combination of separation and exclusion fears (Lubbe 2003). These twin fears may lead them into hypermasculine behaviors in which they demonstrate the vanquishing of sexual rivals by systematically seducing women, many of whom are already involved with other men. Like his female counterpart, the hysterical male wishes to be the object of desire, and he may go through one relationship after another seeking his "object in waiting," only to find that none of them provides the special affirmation that he requires.

Other adaptations are possible as well. Some men with this hysterical variant of HPD will choose a celibate lifestyle, such as the priesthood, to unconsciously maintain unswerving loyalty to their mothers. Other boys will deal with their perceived genital inadequacy by indulging in solitary hypermasculine activities such as bodybuilding. Thus, they can reassure themselves that they are "real men" with nothing to feel inferior about.

Some of these developmental and psychodynamic issues may emerge only after several months of therapy. A skilled dynamic therapist assesses these various models and hypotheses as the patient's life history emerges and as the patient describes his or her characteristic conflicts in love and work. In addition, psychodynamic therapists place a great deal of importance on the emerging transference and countertransference configurations as valuable sources of information.

Technical Considerations

During the early phases of psychotherapy, the building of a therapeutic alliance should be paramount. Specifically, through empathic listening and a concerted effort to understand, the therapist encourages the patient's capacity to collaborate productively with the therapist. Soon, the patient perceives the therapist as a helping professional with good intentions. A good deal of research suggests that the nature of the therapeutic alliance in the opening phase of psychotherapy is perhaps the best predictor of the outcome of that therapy (Lawson and Brossart 2003; Luborsky et al. 1980; Martin et al. 2000). Building an alliance also requires the study of goals that are consensually held by patient and therapist. These goals may change as the therapy evolves, but the collaborative work around development of the goals certainly lays the groundwork for an alliance in the examination of difficult and painful feelings.

The global impressionistic cognitive style is intimately connected to the defensive repertoire associated with patients on the hysterical-histrionic continuum. Questions posed by the therapist may be answered in vague and incomplete sentence fragments, as in the following example:

THERAPIST: How was your weekend?
PATIENT: Awful! I don't even know how to describe it.
THERAPIST: What happened?
PATIENT: Believe me, you don't want to know.
THERAPIST: I really would like to hear more about it.
PATIENT: Well, this guy who asked me out turned out to be one of those—you know—one of those—whatevers.
THERAPIST: I really don't know, so please help me understand with a little more detail, if you can.
PATIENT: Well, he was the kind of guy who—I don't know exactly what words to put to it.
THERAPIST: Well, try your best to describe him to me.

As depicted in this transcript of a therapy session, the hysterical or histrionic patient often begins therapy with an unconscious expectation that the therapist should be able to understand him or her intuitively and nonverbally, without the patient's needing to provide details of his or her intrapsychic experience (Gabbard 2014). This expectation may be linked to a poignant wish that the patient's mother and/or father had recognized and understood him or her during childhood. Thus, the expectation of being seen, heard, and understood is fraught with a mixture of hope and disappointment (Riesenberg-Malcolm 1996). As the vignette demonstrates, the therapist exemplifies the emotional aspects of what has been communicated but also conveys that more detail is needed for a complete understanding. This useful technique is designed to encourage the patient to begin to articulate in words what is conveyed in feeling, because the therapist is not able to read minds.

Horowitz (2001) noted that individuals along the hysterical-histrionic continuum inhibit information processing to blunt strong emotions. Repression, denial, dissociation, and suppression are defensive strategies that all serve to reduce emotional arousal. He stressed that patients may say "I don't know" when what they really mean is "I must not know" (Horowitz 1997). The inhibition of emotional arousal typically oscillates, with exaggerated emotional displays designed to elicit responses from others. Hence, in a paradoxical sense, exaggerated emotionality may defend against more authentic forms of affective expression.

Therapists must learn to be patient with the intense emotional displays. Although it may be tempting to react with dismissiveness or contempt, it is useful to remind oneself that something terribly important is being communicated in the hyperbolic affective mode displayed by patients with HPD. These patients are terribly concerned that they will be ignored or not taken seriously. The desperation they feel often stems from childhood, where they could not gain the attention they needed from parents, and they assume that the therapist will ignore them in the same way. The emotional intensity is an attempt to communicate to the therapist, "Please recognize me! Please tune in to my pain!" The paradox, of course, is that exaggerated emotions may actually lead others to become less attentive, so the therapist also must help the patient understand that more subdued modes of expression may actually result in greater success interpersonally.

A key component of psychotherapeutic technique with patients along the

hysterical-histrionic continuum is to encourage them to *reflect* rather than simply emote. In this way, therapists convey that it is of value to look inward and try to articulate what the patient's internal world is telling him or her. Often, the therapist must assist by making his or her own observations, as in the following example, where a patient with HPD begins the session sobbing:

THERAPIST: You seem incredibly upset today. What's going on?
PATIENT: I hate myself!
THERAPIST: Can you try to put the tears into words?
PATIENT: I don't know.
THERAPIST: Can you look inside and tell me what experiences or ideas about yourself are related to your tears?
PATIENT: I'm not sure.
THERAPIST: Well, from my vantage point, you look more angry than sad. Is there someone you're angry at?
PATIENT: I think I'm mainly angry at myself.
THERAPIST: What did you do that makes you so angry at yourself?
PATIENT: I let myself get suckered in by another sleazy guy.
THERAPIST: Tell me what your understanding is of that. How is it possible that he was able to "sucker you in"?

In this vignette, the therapist tries to give words to the patient's feelings based on observations from an outside perspective (Gabbard 1997). The internal experience of patients with HPD is often one of being buffeted by powerful emotional forces beyond their control. There may be no apparent connection between feeling states and ideas. Therapists help the patients retrieve the ideational connection to feeling.

Over time, patients in the histrionic spectrum who stay in psychotherapy begin to identify feelings, attitudes, and ideational states so that they develop a greater sense of self as agent in effective interaction with the environment rather than self as passive victim of the environment (Gabbard 2014; Horowitz 1977). As these patients begin to attend in greater detail to their inner worlds, they begin to understand the self as it operates in an interpersonal context. They may perceive relationships as following patterns that are repeated again and again in their mode of relatedness to others. Hence, they understand that they play an active role in perpetuating certain patterns of relating to others rather than simply being victimized by the mistreatment of others. They can also develop a capacity to compare the actual facts of an interpersonal situation with the internal patterns superimposed on events and persons.

In the psychotherapy of the higher-level histrionic patient, therapeutic work within the transference may be a primary vehicle for change. A fundamental psychodynamic concept is that patients recreate their internal object worlds in their relationship with the therapist. Hence, what the therapist regards as character is in part a particular mode of feeling that the patient imposes on the therapist. For example, patients with histrionic features will want to cast themselves in the role of the other's object of desire. Therefore, they will use seductiveness and often exhibitionistic displays to rivet the other's attention in an erotized way. Therapists may feel sexual desire or a wish to rescue the patient as a result. These patients may also attempt to capture the therapist's desire by becoming exactly what they think the therapist wants them to be. A common variation of this is trying to become the perfect patient who will think psychologically and flatter the therapist with compliments about

the therapist's technique. Therapists may find themselves looking forward to seeing these patients and may find them fascinating, engaging, or enticing.

As noted in the introduction to this chapter, these transference-countertransference constellations may vary depending on where the patient resides on the histrionic spectrum. The higher-level patient tends to be developmentally more advanced and therefore ensconced in triangular oedipal relationships. Hence, the patient has an acute awareness that the therapist is connected to a third party who is not in the room. This awareness makes the patient more anxious and ashamed about having erotic longings. The therapist is seen as an unobtainable object of the patient's desire, and the very impossibility of the situation is more exciting to the patient.

By contrast, the patients with the more primitive variant may be much less aware of triangular oedipal relationships. They may think that they exist in a bubble alone with the therapist, without any third party near. They may think that there is a real possibility of having a sexual relationship with the therapist and make a tenacious and ego-syntonic demand for sexual gratification. Those with histories of childhood sexual abuse may be particularly prone to behave in this way. Transference interpretation may fall on deaf ears with these patients because they lack the reflective distance from their feelings to see them as part of a pattern. They may do better with a mentalizing approach that teaches them to reflect on their own and others' feelings as fundamentally subjective and based on their past experiences, beliefs, and culture.

Because absence is erotized in hysterical patients, psychotherapy is a situation that is inherently stimulating. The absence of physical intimacy in the therapeutic situation, with a separation at the end of each hour, will be regarded as continually exciting by many histrionic patients. Some may even develop what Bollas (2000) referred to as *transference addiction,* because the therapy is experienced as an exclusive relationship. They may wish for the therapy to go on forever and have no interest in terminating.

One of the common errors in the handling of erotic or erotized transference is to prematurely interpret the transference as a way of making it go away. Often, the therapy benefits from allowing therapist and patient to stay steeped in these feelings over an extended period of time to more fully understand the multiple meanings of the transference. There is often a dark side to erotic transference in which feelings of aggression are intimately linked to the loving feelings. After all, acting on sexual feelings in the therapeutic context can destroy the therapist's career and seriously damage the patient's trust in the therapist. Hence, therapists are advised to matter-of-factly explore erotic transferences in terms of their multiple functions and meanings.

Cognitive Therapy

Core Concepts

Cognitive therapy was originally designed to treat depression, but in recent years it has been expanded in theory and technique to address personality disorders (Beck et al. 2004; Freeman et al. 2005). The basic premise of cognitive therapy is that people attach idiosyncratic meanings to events and people in their lives and that these meanings shape their feelings and behavior. Different people may attach different meanings to the same stimuli and events because of the way they process information (Beck et al. 2004). In other words, environmen-

tal experiences, in concert with genetic predispositions, combine to form schemas—that is, cognitive structures that assign meaning to events through the manner in which information is interpreted. From this perspective, disorders of personality can be understood as arising from negative schemas that begin early in development and cognitive errors and judgments that are consistently biased. This biased information processing, along with negative core beliefs about the self, others, and relationships, colors the individual's motivations, produces patterns of emotional response, and narrows the individual's repertoire of reactions to a restricted set of overused behavioral and affective dispositions (Beck et al. 2004). These characteristics create the core features of personality disorders.

Patients with other psychiatric disorders may have dysfunctional beliefs, but patients with personality disorders maintain their core beliefs with greater intensity. These beliefs are not only more tenaciously held but also more long-standing and more influential on the way the world is perceived. They have become ingrained over time, and the patient is likely to see them as unimpeachable, rather than pathological, in many cases.

The Personality Belief Questionnaire (PBQ; Beck and Beck 1991) is a self-report instrument designed to assess dysfunctional beliefs associated with personality pathology. PBQ analyses indicate that the instrument is best described by seven empirically identified factors, six of which assess dysfunctional beliefs associated with forms of personality pathology recognized in DSM-IV (American Psychiatric Association 1994). Responses on the PBQ from 1,121 outpatients were analyzed in the context of DSM-IV personality disorder diagnosis (Fournier et al. 2012). Subsets of patients who were diagnosed with specific DSM-IV personality disorders scored higher on specific factors from the PBQ. The investigators in this study determined that the identification of core dysfunctional beliefs may aid in case conceptualization and provide targets for psychotherapy.

Technical Considerations

Cognitive therapy proceeds by targeting the core beliefs that haunt the patient with HPD. The PBQ study by Fournier et al. (2012) identified, through factor analysis, several dysfunctional beliefs held by patients with HPD. These include the following: 1) If I don't keep others engaged with me, they won't like me; 2) Unless I entertain or impress people, I am nothing; 3) The way to get what I want is to dazzle or amuse people; 4) In order to be happy, I need other people to pay attention to me; 5) If I entertain people, they will not notice my weaknesses; and 6) It is awful if people ignore me. These characteristic dysfunctional beliefs are in every case linked to schema involving how others are likely to react to the individual with HPD.

The first step for the cognitive therapist is to prepare a case conceptualization (Beck et al. 2004). This formulation conveys the therapist's understanding of the patient's problems while also identifying the beliefs and schemas that need to be addressed. In conjunction with the patient, the therapist establishes short-term, intermediate, and long-range goals. An overarching goal is to help the patient recognize these dysfunctional beliefs and think in a more realistic and adaptive way. A common way to begin is to proceed with cognitive reframing, a standard technique in cognitive therapy.

To facilitate cognitive reframing, the therapist may ask the patient to keep a thought record between sessions that will identify automatic thoughts, which are related to the dysfunctional beliefs

noted above. The therapist would then help the patient evaluate the automatic thoughts through questioning, considering alternative explanations, and examining the evidence to determine the interpretation that is most in keeping with the data at hand. The therapist might also propose behavioral experiments where the patient is invited to test assumptions in the context of exposure to anxiety-producing situations. The patient may be given the task of checking out how he or she is coming across to others. Role-playing is another technique used in cognitive therapy to practice potential interactions within the therapy where different responses can be considered. Another overall goal is to activate and develop realistic beliefs. As problems arise, the therapist engages the patient in a problem-solving approach.

Cognitive therapy promotes the development of a new frame of reference (Beck et al. 2004). As patients engage in the techniques described, they begin to recognize that their behaviors and reactions grow out of dysfunctional beliefs. Soon they develop the capacity for "distancing"—that is, the ability to be more objective about their automatic thoughts and recognize them as beliefs rather than indisputable facts. They also learn through exposure to anxiety-provoking situations that the threat is unreal, or at least exaggerated.

The patient with HPD who believes, for example, that unless he entertains or impresses people, he is nothing, learns that many people in his circle will actually express the same positive views toward him regardless of how he behaves.

Group Psychotherapy

As a general principle, patients on the hysterical-histrionic continuum in their pathology will do well in a heterogeneous group therapy setting. However, patients with HPD who are close to the borderline spectrum may feel that they are not getting sufficient attention in a group. The other patients in the group can often support such a patient and help the patient feel that he or she belongs, especially if the patient with HPD is in a concomitant individual therapy process. Patients with the neurotic (hysterical) variant of HPD may actually become leaders in their groups (Gabbard 2014). Other group members may be impressed at the extent to which they can express their feelings and offer help to other patients in the group. The group modality is particularly useful in helping patients with HPD see how they unconsciously are seductive toward others and create feelings in those around them of which they are not aware. For example, a male histrionic patient was told by three different female members in his group that he always seemed to be "hitting on" women when he talked to them. He seemed genuinely surprised and thought he was just being friendly. Histrionic patients may view the group as an opportunity to receive maternal nurturance that was missing in childhood, and they often become loyal and attached members.

Conclusion

The diagnostic category of HPD subsumes a spectrum of patients with varying levels of organization. A careful assessment of a patient's intrapsychic strengths and weaknesses is crucial in tailoring the psychotherapeutic approach to the individual. No data from controlled trials specifically focused on HPD are available to substantiate the efficacy of any particular psychotherapy. However, clinical wisdom suggests that both psychodynamic and cognitive-behavioral

approaches may be useful. The problematic personality traits of patients with HPD are entrenched and long-standing, so most experts concur that brief psychotherapy is probably not sufficient to make lasting changes in patients on the histrionic-hysterical continuum.

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CHAPTER 72

Narcissistic Personality Disorder

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Over the years, understanding of narcissism and narcissistic personality disorder (NPD; American Psychiatric Association 2013; see Box 72–1) has significantly increased. The introduction of a self-regulatory model for pathological narcissism, which captures the range from self-enhancement to inferiority and vulnerability, has opened new perspectives on approaching and understanding narcissistic personality functioning. The concept of self-agency has helped in integrating observations of the functional fluctuations, need for control, and interpersonal distancing that are typical for narcissistic patients. Recent neuroscientific research on empathic capability and emotion recognition has also added to the understanding of functional patterns and limitations in patients with NPD. Empathy is a capability with deficiencies and areas or moments of fluctuations, as well as with interactive functional components. The latter include emotion recognition and comprehension, and attunement to emotional experiences in both self and others—all affecting self-esteem regulation. Recognizing this can help in further understanding of NPD and in developing more appropriate therapeutic interventions.

Box 72–1. DSM-5 Diagnostic Criteria for Narcissistic Personality Disorder

301.81 (F60.81)

A pervasive pattern of grandiosity (in fantasy or behavior), need for admiration, and lack of empathy, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Has a grandiose sense of self-importance (e.g., exaggerates achievements and talents, expects to be recognized as superior without commensurate achievements).

2. Is preoccupied with fantasies of unlimited success, power, brilliance, beauty, or ideal love.
3. Believes that he or she is "special" and unique and can only be understood by, or should associate with, other special or high-status people (or institutions).
4. Requires excessive admiration.
5. Has a sense of entitlement (i.e., unreasonable expectations of especially favorable treatment or automatic compliance with his or her expectations).
6. Is interpersonally exploitative (i.e., takes advantage of others to achieve his or her own ends).
7. Lacks empathy: is unwilling to recognize or identify with the feelings and needs of others.
8. Is often envious of others or believes that others are envious of him or her.
9. Shows arrogant, haughty behaviors or attitudes.

Paired with accumulating psychoanalytic accounts on treatment of patients with pathological narcissism or NPD, alternative strategies for alliance building and interventions have gradually developed. Applying a dimensional perspective with a conceptualization of pathological narcissism and NPD in terms of self-regulation can potentially further guide the clinician at an early stage in treatment to focus on patients' sense of identity and agency, fragility in self-regulation, self-protective reactivity, and range of self-enhancing and self-serving behaviors and attitudes. Modifications of the evidence-based treatment strategies that have proven beneficial for the near-neighbor borderline personality disorder have turned out to be useful for some patients with NPD as well. However, at this point, continuing exploration of the range and complexity of narcissistic functioning and integration of suitable and effective treatment modalities and strategies still remain works in progress.

Self-Regulation and Fluctuations in Narcissism and NPD

Healthy narcissism and pathological narcissism coexist in complex ways in each individual and vary depending on a person's environmental stress and internal subjective experiences of interpersonal and life circumstances. Narcissistic self-regulatory fluctuations and accompanying shifts in self-esteem are context dependent and affected by situational reactivity. It is not always clear and easy to discern where healthy proactive or maybe somewhat excessive narcissism ends and pathological narcissistic self-enhancement begins. It also is not always easy to determine where temporary pathological narcissistic self-enhancement ends and more enduring, stable, and pervasive character pathology takes over. In addition, what can be indications of pathological narcissism in one context can in another represent healthy, protective narcissistic functioning.

Pathological narcissism, identified as dysregulation of self-esteem, affects, interpersonal relations, and at times superego, covers different degrees of severity and levels of function. Some people can present with consistent or intermittent high functioning and professional or social success, or with exceptional capabilities. Strengths and abilities in certain areas can help sustain self-esteem and interpersonal functioning, as well as protect vulnerabilities and predisposition for narcissistic reactivity. Capacity for continuous and evidence-based vocational or creative work, maintained

over time, both in phases of success as well as setbacks, is a significant indication of sustainable higher functioning in persons with NPD. Others can have a history of occasional or irregular accomplishments, and some present with more severe functional impairment and disabling narcissistic traits (Stinson et al. 2008), especially when NPD is co-occurring with major mental disorders such as substance use, mood or anxiety disorders, somatic conditions, and psychosis with grandiose delusions. NPD can also co-occur with antisocial and sociopathic functioning, or take the form of malignant narcissism with severe psychopathic aggressive and destructive tendencies.

Suicidality is yet another condition associated with subjectively experienced severe narcissistic trauma, entrapment, and losses. When co-occurring with other forms of character pathology or major mental disorders, such as borderline, histrionic, or obsessive-compulsive personality disorders, or the bipolar spectrum disorders, eating disorders, substance dependency, or posttraumatic stress disorder, pathological narcissism and NPD can have major implications for course and prognosis. Mental conditions and symptoms can take on narcissistic meaning, such as superior control of extreme low weight, or have self-regulatory functions, such as the welcome effect of elevated mood on self-esteem, energy, and achievement (Ronningstam 2005).

Initiating Treatment and Building an Alliance

Persons with pathological narcissism or NPD seek treatment for various reasons and in different faces or contexts in life (Table 72–1). Their level of motivation varies greatly depending on such factors as experiences of urgency or being caught in a trap, capacity for insight, affect tolerance and regulation, and the absence or availability of outside sources of narcissistic gratification that support a continuation of the patient's narcissistic views and lifestyle.

Several narcissistic features and patterns can contribute to the patients' initial caution and guarded or even deceptive presentation. These include perfectionism, superiority, and other self-enhancing strivings; limited ability or willingness to self-disclose and self-reflect; shame and dread of facing intimidating or deflating exposure; and expectations of being accused, blamed, and devalued. Difficulties acknowledging and verbalizing internal subjective experiences reflective of patients' narcissistic functioning can cause obstacles in alliance building and long-term treatment progress. Such experiences include sense of worthlessness and incompetence; fear of loss of self-agency, competence, and sense of control; and dread of loss of status, affiliation, and special support. People with NPD can also be unable or unwilling to identify or experience their character traits as problematic. Circumstances and relationships that support or enhance their self-esteem may convince them that they function well. In addition, compromised empathic capability and emotion recognition (Marissen et al. 2012; Ritter et al. 2011) can cause both self-reflective and interpersonal obstacles in alliance building and processing of treatment interventions. The following vignette illustrates a complex narcissistic self-regulatory presentation.

> Mr. M convincingly told his new therapist that he was sure he had NPD. He had also confirmed this through Internet research and reading a number of books. He said, "I am entitled and believe I should be granted much more in life than I have. I despise and devalue all my girlfriends after a few

TABLE 72–1. Patients with narcissistic personality disorder in treatment

Reasons for seeking treatment	Problems, complaints, and symptoms	Personal functioning and life circumstances
Ultimatum or requirements from family, employers, or courts	Denial or lack of awareness of own problems or suffering; unassuming naivete; projection or blame of problems onto others	Consistent self-enhancing or narcissistically sustained functioning; fluctuations in vocational/professional performance, or in collaborative or interpersonal/intimate functioning
Dissatisfaction with life; unable to reach or pursue goals or aspired accomplishments	Absence of major external problems; inner emptiness, meaninglessness, dysphoria, inability to form or maintain close relationships, social isolation; facing limitations or inability to reach goals in personal or professional life	Consistent or high functioning with self-regulatory sustaining interpersonal and/or vocational ability, areas of success or recognition; internal doubts, self-criticism, distancing and detachment
Acute crises; vocational, financial, or personal failures or losses	Rage outbursts, sexual dysfunction, situational anxiety, insecurity, inferiority, shame, fear	Sudden or gradually developing corrosive life circumstances
Major mental disorder; acute or gradual onset of bipolar disorder, substance abuse, posttraumatic stress disorder, or major depression	Depression, anxiety, rage or mood lability, growing dependency on alcohol or drugs, sudden memory flashbacks or intrusive thoughts	Self-enhancing function of mood elevation or substance use; reoccurrence of narcissistic trauma; sudden or gradual functional decline
Suicidality; acute serious suicidal preoccupation; having survived a lethally intended suicidal effort	Internal despair, fear, overwhelming shame and humiliation, worthlessness, rage	Job loss, financial crises, failed promotion, divorce, loss of significant sustaining attachment or self-regulatory support; other subjectively traumatic or severely humiliating experiences

> dates, and I think I am much smarter than my colleagues, but I also resent them for advancing faster and further in their careers than I do. I went to one of the best universities in the country, and I believed that would grant me an international top job, but it didn't. My previous therapists have all confirmed my narcissistic trait and tendencies. They have said that it is as if I see the stop sign but I don't stop because I don't think I need to, or I don't want to. I know I should, but I resent subordinating myself." Then he looked at the therapist with a satisfying smile and asked, "So what can you do about this? It is your task to fix me; you are the expert."

Patients with pathological narcissism or NPD can present with difficulties identifying meaningful specific problems. They may not know what their problems are, why they seek treatment, and what they want to work on, or they may see a discrepancy between their own and others' perceptions of their problems and what they need to change. They often feel blamed, threatened, and unfairly treated, and they readily oppose and criticize their therapists' comments and interventions, or they ignore or dismiss them while pursuing their own points of view. They use various more or less effective ways to enhance their self-esteem, sustain perfectionist ideals, and avoid embarrassing exposure of failure. One such way is for them to identify with the therapist, taking on his or her vocabulary, perspectives, and interventions as their own, while on a deeper level remaining distant and unchanged.

Building a therapeutic alliance, especially with patients presenting with pathological narcissism or NPD, is a gradual process with inevitable challenges and obstacles (Bender 2005; Ronningstam 2012; Safran and Muran 2000). Patients with NPD are known to prematurely drop out of treatment, and alliance and collaborative resistance and ruptures are usually more present than absent. Alliance building is affected by internal and interpersonal traits and experiences. For patients with NPD, those traits and experiences can include perfectionism, psychological trauma, and suicidality (Hewitt et al. 2008; Maldonado 2006; Weinberg et al. 2011); harmful substance use (Tatarsky and Kellogg 2010); comorbid borderline personality disorder (Diamond et al. 2012); and antisocial or psychopathic features (Kernberg 1984). In addition, external life conditions—either sustaining and self-enhancing conditions or conditions that are threatening or failing to support narcissistic functioning—affect patients' motivation and alliance building as well.

An initial task in the alliance building is to identify specific, mutually agreed-upon goals and targets for exploration within a clearly outlined treatment frame and contract. A flexible and balanced alliance-forming and therapeutic stance is required. A patient's strengths and capabilities and wish for personal growth, as well as the adaptive and protective functions of narcissistic self-enhancement and defenses, have to be identified, in addition to the person's fragile self-esteem, reactivity, vulnerability, and need for internal control.

Active involvement and collaboration in treatment usually require abilities that individuals with NPD may be lacking, such as capacity for symbolization and mourning (Kernberg 1993) and tolerance of fear and psychic pain. These patients tend to deny or close off awareness of deeper internal conflicts, threatening affects, or external circumstances. These traits, combined with the patients' capacity for balancing partial participation with partial detachment or tempo-

rary withdrawal in the treatment alliance, contribute to certain oscillations in the patients' ability to collaborate with the psychotherapist. It is important to acknowledge both the patients' urge to reject and their wish to preserve other people—including the therapist—in their lives. The patients stand between the need for protection and withdrawal on the one hand and the necessary but frightening challenge of emotional engagement in the therapy on the other.

Self-critical, self-shaming, and severely harsh self attacks for not meeting standards of superiority or perfectionism tend to undermine the ability of patients with NPD to relate and collaborate. In particular, intelligent and gifted young patients with NPD with an impairing comorbid condition can present such challenges: although they can have extraordinary capability (i.e., being "straight A" graduates who believe that the world opportunities are waiting for them), they also can be unable to hold a job, struggle with body image and eating disorder or substance dependence, and feel guilty and confused and ashamed for not being able to do better in life. Careful attention to the nature of patients' conscience is also necessary. For some patients, dishonesty, as well as deliberate omissions or episodes of fraudulent or illegal self-enhancing behavior, can escalate during difficult phases in the alliance building.

Challenges in Treating the Narcissistic Patient

Sudden dropout and premature termination are common indications of some of the specific challenges in treatment of patients with pathological narcissism and NPD. Such disruptions often relate to the patient's psychological investments in split-off interpersonal relationships or internal experiences. Involving the treatment alliance and/or life circumstances outside of treatment, such investments may take a long time to discover, especially if the patient is functioning well and demonstrating change in some areas. However, over time there can be more or less clear indications that changes are only partial and not involving deeper or more significant conflicts and narcissistic self-regulatory patterns. Changes toward either worsening or improvement in narcissistic functioning often relate to real-life experiences that can be either threatening and corrosive, or corrective and promoting (Ronningstam et al. 1995, 2008). Similarly, developmental life changes (marriage, childbirth and rearing, retirement and aging), as well as sudden unexpected life events in professional, financial, or interpersonal contexts, can drastically impact people with narcissistic vulnerability. Outside events or sudden life changes can drastically affect the therapeutic alliance. Sometimes, conflicts, internalized object relations and representations of self or others, or past traumatic experiences, any of which have been masterfully kept aside through effective narcissistic self-regulation and defenses, can unfold in such moments and unexpectedly move treatment forward. At other times, such events and changes may make the treatment unbearably difficult for the patient and lead to disruptions or premature termination.

Given the presently overloaded meaning and reaction to the NPD diagnosis in society, the integration of the diagnosis of NPD in the treatment process can be complicated. The one-sidedness of the trait-focused diagnosis—that is, not acknowledging the patients' range of functioning, including vulnerability, internal anguish, shame, and fear—remains a problem,

with potential negative implications for the treatment. As presently worded, narcissistic traits such as grandiose sense of self-importance, entitlement, lack of empathy, and so on, can indeed be experienced as more provocative and shaming than informative and guiding for patients' progress and change. Or these traits can even be impossible to identify in a meaningful way for both the patient and therapist. For alliance building and for enabling a gradual change process in the treatment, it is very important that there be a meaningful link between patients' personal experiences of their problems and the defining characteristics and description of the disorder, especially in treatment modalities that focus on target behavior (dialectical behavior therapy, cognitive-behavioral therapy). Objectifying interpersonal perspectives of patients' behavior that override their own subjective internal experiences may turn therapeutic efforts antagonistic and lead to the opposite, escalating narcissistic defensiveness and premature termination. Psychoeducation and clarification of narcissistic personality functioning can, therefore, be most productive additions to regular treatment interventions.

Some patients seek individual psychotherapy after several efforts with different types of modalities or therapist styles. An outstanding pattern in many such patients (like Mr. M, introduced earlier in "Initiating Treatment and Building an Alliance") is their way of skillfully adopting therapists' comments and interpretations—that is, internalizing the therapist's perspectives, without changing their own, and without incorporating the therapeutic process to generate change or cure in their own personality functioning. Conceptualized as *reversible perspective* (Bion 1963; Etchegoyen 1999), and opposite to insights that can induce change, this is one of several complex obstacles in alliance building with narcissistic patients. A conditional and limited alliance is unfolding, which can seem collaborative and interactive with common language and processing of sophisticated interpretations; however, the patient's motive for being in treatment may be totally separated from achieving changes or modifications of essential areas of pathological narcissistic functioning.

Fear avoidance, especially fear of failure, intense emotions, and loss of control, is a common defensive maneuver in patients with NPD, and is now recognized as an important achievement motive and self-regulatory strategy (Bélanger et al. 2012). Doubts, shame and insecurity, confused self-identity, and self-criticism contribute to vulnerability in narcissistic patients and to their sometimes drastic self-regulatory stands. For example, they can strive to make the therapist feel chosen, competent, and specially relied upon, or they may even, like Mr. M, try to present themselves as perfect narcissistic patients, meeting all significant criteria for NPD, in order to avoid the underlying fear of loss of an enhanced self-image and the accompanying sense of failure and inferiority, and feelings of shame, rage, and envy. Life circumstances, age, and maturity also play a significant role in narcissistic patients' perception and tolerance of fear. It is still unclear how much limitations in affect tolerance or recognition, especially of fear, shame, and rage, indeed contribute to this characterological armor.

Narcissistic patients who struggle with suicidal ideations present a specific challenge for the clinician. With such patients, it is very important to differentiate between life-threatening versus life-sustaining implications of their suicidal thoughts and fantasies (Maltsberger et

al. 2010). For some individuals, suicidal ideas and fantasies can actually serve a narcissistically useful function and indeed help keep them alive. The difficulty is determining when a narcissistic patient's suicidal preoccupation represents a life-threatening state, spurred by despair and intolerable emotional suffering, signaling an ongoing ego regression and risk for self-breakup, or when such thoughts in fact are sustaining and serving a narcissistic self-regulatory function that actually can help the patient maintain a sense of control and keep unbearable feelings away. Facing corrosive life events or warning signs of potential or real threat and loss can instantly evoke such overwhelming despair that suicide for the patient becomes the only way out (Ronningstam et al. 2008). On the other hand, for individuals with a sturdy ability to differentiate subjective internal reality from external, action-based reality, knowing that suicide is a possible option can indeed serve as a long-term self-regulatory approach, and help them stay connected, work and function, and even enjoy life. In patients with more severe, malignant narcissism, revengeful, retaliating, or triumphal suicidal fantasies can serve to control their hatred or sadism, but if such thoughts are intensified, they can also instigate suicidal action (Kernberg 1992). A careful and balanced therapeutic strategy is needed that aims at exploring and differentiating internal narcissistic self-regulation from experiences or anticipations of external narcissistic threats. The therapist's task is to identify the function of the suicidal ideations—that is, temporary (like a warning signal), or regulatory (useful to have access to), or intentionally lethal (readily turning into action)—and either help the patient to strengthen sustaining, protective narcissistic ego functions and defensive self-regulation, or implement connective structure or urgent care.

Treatment Modalities

So far, no single treatment strategy has proven superior or reliable with patients with NPD. The range and fluctuations in these patients' functioning have made it more important to adapt a flexible treatment approach and adjust treatment strategies in accordance with their functioning and abilities. Treatment modalities and strategies with specific focus on pathological narcissism and NPD are listed in Table 72–2. None has so far been empirically tested for evidence of efficacy. Many documented accounts of treatment of NPD with various approaches have accumulated and indicated specific treatment-related directions and their pros and cons.

Psychoanalytic Approaches

Psychoanalysis

Psychoanalysis has long been considered a treatment of choice for people with NPD (see chapters in previous editions of this book for detailed reviews: Groopman and Cooper 1995; Ronningstam and Maltsberger 2007). The three most comprehensively outlined are the self-psychological (Kohut), the ego-psychological object relational (Kernberg), and the interpersonal (Fiscalini). Four to five sessions per week over several years is recommended for highly motivated patients with NPD who have good capacity for free associations, insight, and interpersonal relatedness with high affect sensitivity and tolerance. For some patients, however, traditional psychoanalysis may provide a holding structure

TABLE 72–2. Treatment modalities outlined specifically for narcissistic personality disorder

Treatment modality	Goals and strategies
Psychoanalytic approaches	
Kohut's self psychology (Kohut 1968, 1971, 1972)	Encourages grandiosity and idealization in the transference; strives for understanding of empathic failures in the therapeutic alliance; uses an active interpretative strategy, focusing on mirroring, idealization, and twinship
Kernberg's ego-psychological object relations (Kernberg 1967, 1975, 1984)	Uncovers the negative transference and the pathological grandiose self, interpretation of grandiose defenses, and pathological idealization; focuses specific attention on the countertransference for understanding the patient internalized split off representations
Fiscalini's Interpersonalists (Fiscalini 1994; Fiscalini and Grey 1993)	Explores the evolving narcissistic transference-countertransference matrix as well as the healthy narcissistic parts of the therapeutic relationship using co-participant inquiry; reintegrates the patient's core needs of mirroring and idealizing approval; focuses on repair of deep feelings of inadequacy and worthlessness
Psychodynamic approaches	
Transference-focused psychotherapy (Kernberg et al. 2008; Stern et al. 2012)	Focuses on mental integration of extreme representations of self and others in self-object relation dyads (unstable, undifferentiated, unintegrated, inflexible), neutralizing the pathological grandiose self; increases tolerance of negative affect, and improves capacity for work and interpersonal relationships
Cognitive-behavioral approaches	
Schema-focused therapy (Young and Flanagan 1998; Young et al. 2003)	Focuses on early maladaptive schemas regarding self and relationship to others; provides reparenting relationship; strengthens healthy adult personality functioning
Metacognitive interpersonal therapy (Dimaggio and Attinà 2012)	Focuses on recognition and awareness of functioning and mental states; gains change by identifying normal grandiosity, stimulating distance to old behavior, and building new schemas for thinking, feeling, and interpersonal relationships that promote agency and autonomy

that paradoxically, while improving awareness, also protects the patients and prevents them from accessing and addressing certain areas of pathological narcissistic patterns. In other words, deeper aspects of a patient's self-sustaining regulation may be "contained" or "out of reach" in the absence of face-to-face interaction, leading to partial or pseudo progress or stalemates with lack of deeper characterological changes.

Intensive Psychoanalytic Psychotherapy

Intensive psychoanalytic psychotherapy, involving two or three weekly sessions with the therapist, is indicated for patients with more severe narcissistic symptoms who are suffering acute consequences of their symptoms and whose characterological functioning requires a more active, interrelational approach. By focusing on both present and early-life experiences, the therapist attends to interpersonal and internal aspects of a patient's conflicts. The relationship between therapist and patient provides indicatives of the patient's underlying or unconscious conflicts that can be explored, interpreted, and understood to improve self-awareness and self-esteem.

Psychodynamic Approaches

Transference-Focused Psychotherapy

Transference-focused psychotherapy (Kernberg et al. 2008; Stern et al. 2012) attends to patients' narcissistic defensiveness, underlying aggression, enactment of entitlement and grandiosity, and sensitivity to envy, humiliation, shame, and inferiority. It is appropriate for patients who can benefit from an active and interactive exploration, and for whom face-to-face interaction and eye contact are important to counterbalance detachment and emotional disengagement. The strategy is flexible and adaptable to the range and level of narcissistic pathology; a less interpretive technique is used with patients with more brittle personality structure.

Cognitive-Behavioral Approaches

Schema-Focused Therapy

Schema-focused therapy (Young and Flanagan 1998; Young et al. 2003) combines cognitive, behavioral, experiential, and transference-based techniques to work with schema modes. The treatment focuses on changing the patient's intimate relationships, including the relationship to the therapist and other significant relationships in the patient's outside life. The goal of the treatment is to promote a healthy adult mode by helping the patient to repair and regulate significant narcissistic moods. General cognitive and behavioral strategies combined with empathic confrontation and homework assignments are used to address typical narcissistic cognitive distortions such as "black-or-white" thinking, being devalued and deprived by others, and perfectionism.

Metacognitive Interpersonal Therapy

Metacognitive interpersonal therapy (Dimaggio and Attinà 2012) is a manualized step-by-step treatment for NPD that begins with an autobiographical mode to achieve a shared understanding of the patient's problems, and then promotes recognition and awareness of his or her functioning and mental states, interpersonal relationship schemas, and indications of poor agency and acting.

Change is achieved through support of reality and perspective taking, and by identifying normal grandiosity, stimulating a critical distance to old behavior, and building new schemas for thinking, feeling, and interpersonal relationships that promotes agency and autonomy.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (Beck and Freeman 1990) has primarily been applied to borderline personality disorder but can also help some people with pathological narcissism and NPD. Patients with NPD who are more behaviorally and action oriented may find that gaining control of behavior can be most helpful. Three strategies—namely, education, validation, and identifying "target behaviors"—can be useful, especially in conjunction with psychodynamic psychotherapy as part of a multimodal treatment plan. Some persons with pathological narcissism and NPD may find these strategies too superficial and target oriented, or even threatening and intrusive in ways that can trigger protesting, rebellious reactions, or premature termination.

Other Approaches

Dialectical Behavior Therapy

Dialectical behavior therapy (Linehan 1993), originally aimed for patients with borderline personality disorder, incorporates validation as an important therapeutic tool to promote self-identification and acceptance and to potentially help reduce feelings of shame, self-criticism, and self-blame. Agreed-upon symptoms or "target behaviors" are specifically attended to via a weekly scorecard that can provide clear evidence of progress of change. Although this exploratory and skill-focused work can be very challenging for some patients with NPD, for others it can provide clear indications of problems and progress, and hence support the patient's sense of internal control and self-agency.

Mentalization-Based Therapy

Mentalization-based therapy, developed specifically for treatment of borderline personality disorder, focuses on improving the patient's ability to understand the intentional mental states that influence and control human behavior. Mentalization is the capacity to think about mental states as separate from but yet contributing to action, and it helps in perceiving and interpreting one's own and others' behavior in terms of intentional mental conditions (Bateman and Fonagy 2004). Mentalization-based therapy has been used for treating high-achieving professionals who are in crises or struggling with perfectionism and need for external validation, or who have underlying vulnerability and fear of losing control (Beliberg 2006). Mentalization can improve one's sense of agency by increasing the individual's understanding and control of emotions and intentions. However, for individuals with NPD who defensively use cognitive empathy and perspective taking for self-enhancing purposes, mentalization may not lead to change. Similarly, individuals with more profound narcissistic fragility and identity diffusion may find mentalization too intrusive and overbearing.

Psychoeducation

Psychoeducation has increasingly been found to be useful in various treatment modalities. Adapted from principles involved in dialectical behavior therapy, psychoeducation for patients with NPD can improve their understanding of their emotional and intrapsychic experiences, which can strengthen their sense of in-

ternal control and agency and decrease their fear of the unknown and loss of control, as well as their fear of feelings and internal mental processes. Psychoeducation can actually promote the patients' motivation and courage to explore deeper emotions and conflicts.

Group Therapy

Group therapy (Alonso 1992; Grotjahn 1984; Roth 1998) can, in conjunction with individual treatment, provide corrective opportunities for addressing shame, self-sufficiency, dependency, nonrelatedness, and narcissistic fantasies. Group settings can gradually challenge and stimulate patients' interactions with others and provide opportunities to learn and practice self-tolerance. The balance between individual and group interests can be challenging for the patients as well as for the group leader.

Psychopharmacological Treatment

In patients with pathological narcissism and NPD, psychopharmacological treatment can be beneficial for comorbid major mental disorders, such as bipolar disorder, major depression, or anxiety disorder. Notably, these patients tend to be hypersensitive to side effects, especially those affecting their sexual and intellectual functioning, which can contribute to the patients' noncompliance or refusal of such treatment. No specific pharmacotherapy has been proven to be effective for pathological narcissism and NPD.

Conclusion

Treatment of patients with NPD is challenging due to complex interactions, fluctuations in functioning, and strong countertransference reactions. A flexible, integrative, and balanced therapeutic stance is recommended, with attention to the adaptive and protective functions of the narcissistic character styles, as well as to the maladaptive, defensive, and self-enhancing traits. At this point, flexibility and integration of modalities can be useful while empirical studies for evidence-based strategies are in progress.

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CHAPTER 73

Cluster C Personality Disorders

Avoidant, Dependent, and Obsessive-Compulsive

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DSM-5 (American Psychiatric Association 2013) describes three Cluster C personality disorders (see Boxes 73–1, 73–2, and 73–3): avoidant personality disorder (AvPD), dependent personality disorder (DPD), and obsessive-compulsive personality disorder (OCPD). These personality disorders generally have less impairment than Cluster A and B personality disorders. Arguably, two personality disorder types, depressive and passive-aggressive, described in DSM-IV-TR (American Psychiatric Association 2000) Appendix B ("Criteria Sets and Axes Provided for Further Study"), as well as one, self-defeating (masochistic), described in Appendix B of DSM-III-R (American Psychiatric Association 1987), could also be included but are mentioned only in passing.

Box 73–1. DSM-5 Diagnostic Criteria for Avoidant Personality Disorder

301.82 (F60.6)

A pervasive pattern of social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

1. Avoids occupational activities that involve significant interpersonal contact because of fears of criticism, disapproval, or rejection.
2. Is unwilling to get involved with people unless certain of being liked.
3. Shows restraint within intimate relationships because of the fear of being shamed or ridiculed.
4. Is preoccupied with being criticized or rejected in social situations.

5. Is inhibited in new interpersonal situations because of feelings of inadequacy.
6. Views self as socially inept, personally unappealing, or inferior to others.
7. Is unusually reluctant to take personal risks or to engage in any new activities because they may prove embarrassing.

Box 73–2. DSM-5 Diagnostic Criteria for Dependent Personality Disorder

301.6 (F60.7)

A pervasive and excessive need to be taken care of that leads to submissive and clinging behavior and fears of separation, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Has difficulty making everyday decisions without an excessive amount of advice and reassurance from others.
2. Needs others to assume responsibility for most major areas of his or her life.
3. Has difficulty expressing disagreement with others because of fear of loss of support or approval. (**Note:** Do not include realistic fears of retribution.)
4. Has difficulty initiating projects or doing things on his or her own (because of a lack of self-confidence in judgment or abilities rather than a lack of motivation or energy).
5. Goes to excessive lengths to obtain nurturance and support from others, to the point of volunteering to do things that are unpleasant.
6. Feels uncomfortable or helpless when alone because of exaggerated fears of being unable to care for himself or herself.
7. Urgently seeks another relationship as a source of care and support when a close relationship ends.
8. Is unrealistically preoccupied with fears of being left to take care of himself or herself.

Box 73–3. DSM-5 Diagnostic Criteria for Obsessive-Compulsive Personality Disorder

301.4 (F60.5)

A pervasive pattern of preoccupation with orderliness, perfectionism, and mental and interpersonal control, at the expense of flexibility, openness, and efficiency, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

1. Is preoccupied with details, rules, lists, order, organization, or schedules to the extent that the major point of the activity is lost.
2. Shows perfectionism that interferes with task completion (e.g., is unable to complete a project because his or her own overly strict standards are not met).
3. Is excessively devoted to work and productivity to the exclusion of leisure activities and friendships (not accounted for by obvious economic necessity).
4. Is overconscientious, scrupulous, and inflexible about matters of morality, ethics, or values (not accounted for by cultural or religious identification).
5. Is unable to discard worn-out or worthless objects even when they have no sentimental value.
6. Is reluctant to delegate tasks or to work with others unless they submit to exactly his or her way of doing things.

7. Adopts a miserly spending style toward both self and others; money is viewed as something to be hoarded for future catastrophes.
8. Shows rigidity and stubbornness.

The treatment literature of Cluster C personality disorders has generally focused on individual psychotherapy and day hospital programs, and to a lesser extent on other treatment modalities such as pharmacotherapy. Most treatment studies have examined the three Cluster C disorders together (Svartberg et al. 2004); mixed in with other personality disorder types (Kvarstein and Karterud 2012; Vinnars et al. 2005) or (rarely) in comparison with one another (Barber et al. 1997), with persons with other disorders receiving the same treatment (Høglend 1993); or as individual disorders (Alden 1989; Emmelkamp et al. 2006). The evidentiary base consists of case descriptions, theoretical pieces, uncontrolled cohort studies, and a modest number of controlled or comparative treatment trials. Across virtually all of these reports, there is an apparent consensus that psychotherapy, in both dynamic and cognitive-behavioral approaches, produces sizable positive effects in patients with personality disorders (Leichsenring and Leibing 2003; Perry and Bond 2000; Perry et al. 1999; Simon 2009). Two related meta-analyses found a number of studies including DPD (a median of 25% with DPD, range 10%–33%) and others with large proportions of unspecified Cluster C disorders (Perry and Bond 2000; Perry et al. 1999). The therapies demonstrated medium to large positive effects (generally larger than 1.0) for individual (Diguer et al. 1993; Hardy et al. 1995; Høglend 1993; Monsen et al. 1995; Patience et al. 1995; Rosenthal et al. 1999; Svartberg et al. 2004; Vinnars et al. 2005; Winston et al. 1991, 1994), group (Alden 1989; Budman et al. 1996), day (Karterud et al. 1992, 2003; Piper et al. 1993; Wilberg et al. 1998), and residential (Krawitz 1997) treatments. A recent meta-analysis specifically focused on the three Cluster C disorders drew a similar conclusion (Simon 2009), noting that most improvement occurred during treatment, with some additional change occurring during follow-up, which was usually of short duration.

The evidentiary base for the pharmacological treatment of Cluster C personality disorders is limited, with most studies focusing on 1) symptom disorders (formerly Axis I conditions), such as generalized or specific social phobia (Allgulander 1999), with indirect relevance to a cognate personality disorder (avoidant); 2) the responsiveness of an Axis I symptom in the context of a cognate personality disorder (Hope et al. 1995) or an unrelated personality disorder (Kool et al. 2003b); or, rarely, 3) the personality disorder itself (Klein et al. 1973).

General Considerations

Attrition From Treatment

Shea et al. (1990) found that Cluster C disorders had lower attrition (28%) by end of treatment than did Cluster A or B personality disorders. Patients with AvPD generally stay in shorter-term treatments, but in the longest treatment duration reported, Barber et al. (1997) found that 46% dropped out before the intended 50 sessions, which contrasted with 7% attrition for patients with OCPD. Karterud et al. (2003) found that those with DPD had lower attrition (16%) from an 18-week day treatment program than all other personality disorder types except schizoid. In a study of

long-term therapy, Perry et al. (2007) found that DPD was the only personality disorder type associated with not dropping out of treatment.

Duration of Treatment

The optimum duration of treatment is not yet known. Eight studies that included only Cluster C disorders had a median treatment length of 22 sessions over 32 weeks, with last follow-up at a median of 58 weeks. Studies that also included personality disorder types from Cluster A or B generally had longer treatment durations. Five treatment studies with nine treatment arms focusing on AvPD used a median of 16 sessions (range 12–35 sessions) over a median of 16 weeks (range 10–64 weeks). Two studies examined OCPD, one of which (Barber and Muenz 1996) focused on treating major depression in patients with OCPD over 16 sessions. The second study (Barber et al. 1997) focused on treating OCPD primarily and used 50 sessions over 52 weeks. No treatment studies focused solely on DPD. However, in a study of open-ended dynamic psychotherapy, my group (Perry et al. 2007) found that DPD and dependent traits were significantly predictive of a median treatment length almost double that in those without DPD (i.e., 129 vs. 66 sessions). By contrast, OCPD was associated with a significantly shorter treatment duration than that for patients without OCPD traits (38 vs. 116 sessions), primarily due to premature terminations. In longer treatments, OCPD traits of perfectionism, devotion to work and productivity, and rigidity are challenges to treatment. In general, reported treatment lengths were insufficient to lead to sustained recovery and development of healthy functioning, although many patients improved significantly or even dropped below full personality disorder criteria. A meta-analysis of Cluster C disorders called for studies of greater treatment duration and longer-term follow-up (Simon 2009).

Cautionary Notes on Interpreting Clinical Trial Results

Compared with borderline personality disorder, Cluster C disorders have relatively few clinical trials. The precision and replicability of findings, as well as the firmness of their interpretation, are limited for the following reasons: studies use different diagnostic methods, sometimes even relying on self-report instruments, which, evidence suggests, have low levels of diagnostic agreement (Perry 1992). Investigators may have strong allegiance to one treatment condition, which in turn influences the design and implementation of the trial favoring that condition, whereas the comparison treatment may be "designed to fail" (Luborsky et al. 1999). Selection of measures influences the magnitude of the effects because some measures, such as target symptoms or distress, are highly changeable, while others, such as interpersonal functioning or core mechanisms of psychopathology, change more slowly (Perry and Sanlian 2002), so an investigator can seemingly enhance treatment effects by avoiding certain measures. This in turn is problematic for meta-analyses, which tend to combine all measures into a mean effect size, rather than analyze effects by specific measures (Perry et al. 1999) or types of measures (Rabung and Leichsenring 2012). Different treatment types may require different treatment durations in the same way that chemotherapy may require a different frequency and duration than radiation therapy for a given cancer. Thus, selection of a given treatment duration

may favor one type of therapy over another (e.g., Emmelkamp et al. 2006; Hardy et al. 1995). Treatment duration and follow-up length may also influence whether highly desirable, delayed treatment effects are detectable (Høglend et al. 2011). Studies vary in whether they assess the proportion of patients who attain sustained recovery or of those who develop healthy functioning (Perry and Bond 2009). Assuming honesty in reporting, one can judge how much weight to give to a trial by taking into account the quality of the study, aided by a recent report of a validated checklist of 24 items assessing quality relating to effect sizes (Thoma et al. 2012).

Intervening Misfortune

A common but unpredictable occurrence in therapy arises when the patient experiences a significant separation, loss, or diminution in personal or financial support, such as unemployment, a severe social setback, or a failure in an important goal. The resulting distress may result in a regression in defensive functioning and overwhelm newly acquired attitudes and skills. There may be increases in dependent wishes, requests, and behaviors in patients with DPD; rigidity, guilt, and counterdependent attitudes in patients with OCPD; and self-deprecation, pessimism, and isolation in patients with AvPD. There may also be accompanying exacerbation or recurrence of comorbid panic, general anxiety, somatic symptoms, or depression. Some regression to levels of functioning prior to treatment is common. This may strain the therapeutic alliance if the patient perceives the therapist as insensitive to his or her emotional reactions, unhelpful, disappointed, impatient, or too demanding of progress. In particular, patients with OCPD may experience intense shame at feeling emotional and helpless and may paradoxically respond to sympathy with anger. The therapist must find a balance between listening, being supportive, and offering some suggestions and direction that the patient will find helpful, while temporarily accepting this interruption in the tasks of growth. In fact, if the therapist negotiates such crises well, the alliance may be strengthened, and the patient, feeling supported and understood, may return sooner than imagined to working on issues of autonomy, separation sensitivity, effective coping, and self-esteem enhancement. Patients with OCPD may also realize that expressing their inner experiences has not had dire consequences and may find relief in experiencing certain affects, such as sadness.

Individual Psychotherapy

Improvement and Recovery

Individual psychotherapy is the most commonly employed and studied modality for Cluster C personality disorders. Sixteen studies with any Cluster C disorders as prominent diagnoses included treatment arms of the following types: 14 dynamic, 9 cognitive-behavioral, 4 interpersonal, 1 mixed dynamic-cognitive, and 1 supportive therapy (Barber and Muenz 1996; Barber et al. 1997; Cyranowski et al. 2004; Diguer et al. 1993; Emmelkamp et al. 2006; Fahy et al. 1993; Hardy et al. 1995; Høglend 1993; Høglend et al. 2011; Kool et al. 2003b; Mersch et al. 1995; Monsen et al. 1995; Muran et al. 2005; Rosenthal et al. 1999; Svartberg et al. 2004; Tyrer et al. 2003; Vinnars et al. 2005; Winston et al. 1994).

The mean number of sessions by treatment type was as follows: 46 for dynamic (range 12–195), 30 for interpersonal (range 16–59), and 17 for cognitive-behavioral (range 5–40). Mean duration of follow-up from intake was just shy of 2 years for dynamic treatments, around 1 year for cognitive-behavioral therapy (CBT), and less for interpersonal therapy (IPT), thus limiting knowledge about long-term effects.

Improvement was universally found in all studies and all treatment approaches. I examined the median effect size for each study arm across all measures used, divided into patient self-report versus observer-rated measures. At termination the median effect size for patient self-report measures across all treatment arms was about 1.2 ($n=18$), whereas at follow-up improvement was maintained with a median effect size of 1.4 ($n=10$). Both figures constitute a large statistically significant amount of change. No study failed to show improvement; the smallest median effect size at termination was 0.44. The figures differ somewhat for observer-rated measures. At termination the median effect size for observer-rated measures across all treatment arms was about 2.3 ($n=13$), whereas at follow-up improvement was largely maintained (median effect size 2.3; $n=3$). Although both figures constitute a very large amount of change, only the termination effect size was statistically significant. Again, no study failed to show improvement; the smallest median effect size at termination was 0.47.

For validated measures with cutoff scores reflecting normal or nonsymptomatic status, the proportion of patients attaining this cutoff could be considered to be recovered. Taking together all of the treatment arms using self-report measures with known cutoffs, the median proportion recovered at termination was about 53% ($n=8$) and at follow-up was 38% ($n=6$). Fewer patients reached recovery across all observer-rated measures, with a median of 38% ($n=11$) recovered at termination and 44% at follow-up ($n=4$). Only the termination figures are statistically significant. Interpretation of these findings requires caution because some measures—for example, the Beck Depression Inventory—are more likely to show recovery than others, such as the Global Assessment of Functioning. Although improvement is greater on observer-rated than self-report measures, the converse is true for recovery. As previously noted (Perry and Bond 2000, 2009; Perry et al. 1999; Rabung and Leichsenring 2012), and convergent with the findings discussed earlier, self-report and observer-rated measures are not directly comparable, complicating comparisons between studies that largely report only one type. Nonetheless, by follow-up fewer than half the patients had reached recovery on a variety of measures. Although, overall, there was little evidence of systematic improvement continuing after termination (i.e., delayed treatment effects), some studies with longer follow-up periods did show such improvement (Cyranowski et al. 2004; Høglend 1993; Høglend et al. 2011). One serious implication is that longer treatment durations, longer follow-up durations, or both should be employed to increase the proportion of patients recovered.

Dynamic Psychotherapy

Whether brief or longer term, time limited or open ended, dynamic psychotherapy is frequently used to treat Cluster C personality disorders. Shorter-term dynamic treatments often have better results when the focus stays more on the patient's external relationships than on

the transference per se. A clear exception arises whenever an impasse occurs, a frequent occurrence for patients with a history of poor relationship patterns. In such cases, exploring the patient's experience with the therapist can improve the alliance and forestall a therapeutic impasse (Høglend et al. 2006), leading to a significantly greater proportion of recoveries from personality disorder on long-term follow-up (Høglend et al. 2011). Some studies indicate that when ultra-short-term therapies are used (e.g., eight sessions), dynamic therapy may be slightly less effective than CBT (Emmelkamp et al. 2006; Hardy et al. 1995). However, most therapists would agree with the data (Høglend 1993) that this time frame is not adequate for the treatment of Cluster C personality disorders.

Avoidant Personality Disorder

In the Treatment of Depression Collaborative Research Program (TDCRP), Barber and Muenz (1996) examined depressed patients with avoidant or obsessive-compulsive personality traits and disorders who completed 16 weeks of therapy for major depression. Avoidant patients did not respond as well to IPT as to CBT. In a trial of 1 year of supportive-expressive dynamic psychotherapy, Barber et al. (1997) found greater attrition among avoidant than OCPD patients. However, effect sizes were still substantial, averaging about 0.99, and 61% of those completing treatment no longer had AvPD by self-report measure. The authors suggested that avoidant patients find unstructured treatment more threatening initially, perhaps leading to a higher early attrition rate, although those remaining in dynamic therapy do quite well. By contrast, Porcerelli et al. (2007), and Presniak et al. (2010) reported a well-documented recovery at year 5 in a single case treated with psychoanalysis over 4 years.

Dynamic therapy requires that the therapist first create a warm, nonjudgmental atmosphere of acceptance of the patient's anxiety, fears of social situations and rejection, and critical view of self. Although some coaching or suggestions may play a role in encouraging the patient to try to interact beyond his or her comfort zone, the therapist should be cognizant of potential pitfalls. These include setting the patient up to fail when the patient does not follow through on a suggestion agreed to in a session. Also, the patient will experience even the most positive suggestions as disappointing, because they have limited impact on the patient's self-critical view and anxiety. Encouraging the patient to explore his or her disappointments or critical experiences of the therapist provides an opportunity to diminish the anxiety associated with criticism. The therapist should take a positive view, occasionally using humor, in acknowledging the therapist's own limitations in providing quick solutions to the patient's painful affective life.

Pushing the patient to pick up the pace of improvement is usually a mistake. Usually, the patient needs to first broaden an understanding of all the factors, present as well as past, relating to feelings of social inadequacy, self-criticism, and sensitivity to rejection. There may be a history of teasing or shaming that leaves the patient highly sensitive to embarrassment. Feelings of social inadequacy may derive from relative parental noninvolvement in which a secure base was never provided or there was little social role modeling. Continual exploration of all of these experiences will allow the patient to diminish self-criticism and develop a more understanding and forgiving attitude toward his or her limitations. As this

process unfolds, avoidance will decrease and the patient will become less resistant to trying new social situations, taking risks in casual interactions, and being open to new experiences.

In the mid-phase of therapy, improvement may be aided when the patient enters some work or social situation that involves frequent contact with a discreet group of individuals. This can be an Internet chat group, an employment program, a group living situation, a social or church group, group therapy, or the workplace. Therapy becomes a safe testing ground for the patient to examine his or her reactions to these people. The repeated social interactions allow the patient to become more comfortable with self-expression, trying and failing, having some rewarding interactions, and then discussing these in treatment. In the context of these settings, the patient can develop a sense of security, which in turn promotes trying new social behaviors and internal exploration of one's reactions. Transferential fears of criticism from the therapist over the patient's failings should also be explored. The therapist inevitably interprets the patient's assumption (projection) of a critical, disappointed, or shaming attitude onto the therapist. As the patient develops insight about the origins of self-criticism and rejection sensitivity, he or she can use more self-observation to suppress the old familiar responses in favor of taking chances on new ones. In this process the patient becomes good at anticipating how he or she might feel ahead of time and subsequently managing situations with greater emotional security. Time until recovery usually requires many months to several years.

Dependent Personality Disorder

Dependent personality was once a great focus of dynamic treatment (Leeman and Mulvey 1975; Perry 2005; Whitman et al. 1954). Despite its prevalence, there has not been a single systematic treatment trial of DPD in recent years, although it is included among studies of the Cluster C disorders.

There is apparent consensus about two central aspects in the dynamic therapy of DPD. The first is that the emergence of a dependent transference toward the therapist should be addressed in a way to promote emotional growth. The second is that therapist expectations and direct support should be used to promote self-expression, assertiveness, decision making, and independence. If both aspects are not addressed, treatment may be incomplete (A.T. Beck and Freeman 1990; Hill 1970; Malinow 1981; Saul and Warner 1975).

As therapy begins, it is important for the therapist to aid the development of a trusting relationship and allow the patient to begin to transfer dependent wishes onto the therapist. If crises or episodes of panic or distress occur early on, Hill (1970) suggested telling the patient that extra sessions may be allowed. This assurance of readily available support helps the patient develop trust and aids alliance formation. As therapy progresses, the therapist may help the patient find substitute ways of dealing with such feelings, limiting extra sessions.

Alexander and Abeles (1968) found that dependency on the therapist increased from the beginning to the middle of short-term therapy and remained fairly high until termination. The high levels of dependency on the therapist necessitated working through transference issues right up until termination. Conversely, the patient's dependency on outside relationships began to diminish from the middle of treatment until termination, suggesting that therapy helped resolve dependency conflicts.

A difficult point in therapy may occur whenever setbacks or losses in the patient's outside life co-occur with increased dependency on the therapist. Offering sympathy for the patient's distress is not by itself helpful (Hill 1970). The therapist should also encourage the patient to express real feelings and wishes, bear the anxiety of making decisions, accept pleasurable experiences, and deal with episodes of anxiety. Whenever the patient experiences frustration with wishes to have the therapist take a directive role, the therapist should explore and interpret the transference elements while advocating finding more self-reliant ways to cope (A.T. Beck and Freeman 1990; Hill 1970; Malinow 1981; Saul and Warner 1975). Limiting attention to transference issues in favor of focusing on outside relationships may be more helpful in shorter treatments of patients with more stable relationships (Høglend et al. 2006; Leeman and Mulvey 1975).

Entering the mid-phase of therapy, the therapist should avoid taking a directive role in the patient's life; otherwise, a transference-countertransference fixation might develop that simply repeats patterns from the patient's other relationships (Leeman and Mulvey 1975; Saul and Warner 1975). The therapist needs to actively resist the patient's repetitive requests for advice and attempts to have the therapist make decisions for the patient, instead helping the patient reflect on how he or she relinquishes responsibility.

Saul and Warner (1975) suggested the following optimal conditions for giving direct suggestions and offering specific actions or solutions to problems: The therapist should, first, have a sufficient understanding of the patient's dynamics and, second, be aware of the state of the transference and his or her own reaction to it. Third, the patient should be at some impasse out of which a direct therapeutic intervention can mobilize the patient, thereby preventing a repetition of feeling powerless. The therapist should help the patient conceptualize his or her own goals. If the goals are healthy, the therapist should discuss and support them. If there are conflicting goals, then it is helpful to discuss the consequences of each goal and to encourage the patient to bear the anxiety of making choices. Although similar to cognitive therapy (A.T. Beck and Freeman 1990), this approach also makes use of previous insights about the patient's motivations. The therapist may then urge the patient to commit himself or herself to actions that are within the patient's reach (e.g., taking a job) or encourage perseverance despite the urge to give up (e.g., flunking out of school). The therapist must also ensure that he or she is using his or her influence in accordance with the patient's own values and not those of the therapist.

Covert dependency on the therapist, in which the patient experiences the therapist as a benign, powerful parent figure (Goldman 1956), can facilitate therapeutic change. The therapist's sincere interest, attention, and reliable presence may increase the patient's belief in the benevolent power of the therapist. This affects the patient's self-esteem in several ways. First, the patient may identify with the therapist and wish to be like him or her (Offenkrantz and Tobin 1974). Idealization leads to a temporary rise in self-esteem. Second, the patient may accept and increasingly use the therapist's exploratory attitude toward his or her emotional life. Third, whenever the patient remembers or experiences hitherto unacceptable feelings for the first time, the therapist should be understanding and accepting. This will enhance the patient's self-esteem, because the patient can identify with the more benevolent

attitudes and responses of the therapist as an authority figure rather than react according to the patient's old prohibitions and ideals. This rise in self-esteem is only temporary as long as it relies largely on the reassuring presence of the therapist. However, if the patient can channel this increased self-esteem to risk trying new behaviors outside the office, he or she may experience other rewards, including approval from others. It is important for the therapist both to communicate genuine pleasure when these outside efforts succeed and to accept failures that inevitably occur. This helps the patient to shift self-perception from dependency toward social self-confidence.

Attending to the patient's defenses can inform the therapist about conflict areas requiring attention (Perry and Bond 2005). Reaction formation against feelings such as anger toward dominant others may be masked as concern for others and submissiveness. Displacement diverts attention away from the patient's problems to those of the people around him or her, subtly externalizing the focus. When needing to act more autonomously and self-assertively, the patient may lapse into help-rejecting complaining, preferring the safer experience of failure while also covertly criticizing others for their lack of care and material help. The therapist should help the patient explore the meaning of such experiences and return to the underlying feelings such as anger, disappointment, and shame. Understanding what makes such affects distressing can then lead to better tolerance of them and point toward more effective functioning.

During the final stage of therapy, the therapist gradually increases the level of expectations for autonomous decision making and action and for socially effective responses (Leeman and Mulvey 1975). The individual receives reinforcement for his or her increasing ability to handle crises without extra sessions and to manage episodes of anxiety or panic by self-soothing rather than by seeking reassurance from others (Hill 1970). The therapist must help the patient to resolve dependent transference wishes and fears of aloneness, powerlessness, and others' intolerance for self-initiated expression and action in favor of accepting a more self-reliant position in relationships. Prior to termination, if the patient avoids mourning the therapeutic relationship—for instance, through a fantasy that he or she was never really close to the therapist or that the therapist will always be available—then termination will spark a crisis. The patient may feel betrayed that the therapist is not available after all, and the patient may begin to deteriorate (Werbart 1997). Even in successful therapies, some symptoms of distress often arise around termination.

Obsessive-Compulsive Personality Disorder

Barber et al. (1997) conducted the only systematic trial of dynamic therapy solely for OCPD. Fourteen patients with OCPD received 52 sessions of time-limited supportive-expressive dynamic psychotherapy. Patients were very treatment responsive, with a mean effect size of 1.29, and only 15% of the patients retained their diagnosis by a self-report measure. It remains doubtful whether observer-rated measures of OCPD would show as dramatic results. Barber and Muenz (1996) examined the TDCRP data and found that among depressed patients with OCPD and OCPD traits, improvement in depressive symptoms was better after 16 sessions of IPT than of CBT. This is congruent with the need for patients with OCPD to explore their affective and motivational lives and relationships as well as to work with maladaptive cognitions.

Although OCPD was mixed with other Cluster C disorders in their study, Svartberg et al. (2004) found that 40 sessions of dynamic therapy and CBT were equally effective in reducing symptoms and improving interpersonal functioning. Dynamic psychotherapy and psychoanalysis are considered by many to be the treatments of choice for patients with Cluster C disorders. Treatments commonly last for longer than 1 year, except when limited to treating a co-occurring episode such as depression. The mean duration of psychoanalysis is 5.7 years (Doidge et al. 2002). Treatment durations for OCPD are not usually on the shorter side of the mean.

DSM-5 reflects the triad of character traits first described by Freud (1908/1959) that make the patient with OCPD difficult to treat: rigidity and obstinacy, excessive orderliness, and parsimony (see Box 73–3 earlier in this chapter). Although these traits may have been adaptive in the childhood environment to minimize criticism or punishment for displays of feeling and autonomy, with attendant anxiety, shame, and guilt, they are very trying for those around the adult patient, including the therapist.

Patients with OCPD often seek treatment because of a symptom or because life seems devoid of interest. Although they can be very appreciative of help during a crisis (when feelings are often more available than usual), after they return to baseline, the pace of therapy slows down considerably. This is because their view of the world and of themselves is egosyntonic; they minimize anything seemingly wrong. To change entails accepting that their categorizations of the world are incorrect. The defenses that underlie these personality features include isolation of affect, intellectualization, undoing, reaction formation, displacement, rationalization, and in some cases devaluation. All of these defenses serve to protect the patient from criticism, disappointment, and the messiness of a full emotional life. The therapist may experience these defenses as impenetrable. Attempts to show the patient an alternate way of viewing or experiencing the world are met with arguments, criticism, and blows aimed at the therapist's self-esteem. When patients with OCPD are subjected to a severe stressor, such as a serious goal failure, or to severe depression, critical views of the self may emerge, and the patients may use devaluation of self-image and projection, revealing a mild paranoid tendency. Whenever suicidal, such patients can be at very high risk because any suicide attempts are often done with thorough planning.

As therapy begins, the therapist must attend to the patient's defenses, recognizing that deep insights are unlikely to emerge early on. Overzealous attempts to enlighten the patient will tax the alliance, because even accurate interpretation is experienced as a criticism and threat. The patient is always on guard against being wrong; this may perhaps even be reflected in a rigid posture, so-called *character armor.* Even minor remarks by the therapist will be subjected to close scrutiny, correction, revision, and dilution before they will be accepted. Reflections, clarifications, and interpretations are parsed to the point that the therapist expects to hear a mantra of "not exactly," "not really," or "I don't think that necessarily follows." If the therapist consistently pushes a point, the patient may resist losing control of the session, by erecting a subtle or overt wall of resistance, or the patient may attack and devalue the therapist's point of view or theoretical approach. For patients with lower levels of object relations, interpretation early on that includes the patient-therapist relationship and transference

may prove crucial for treatment progress. However, for patients with higher levels of object relations, early interpretation of the transference may actually have a mild negative effect (Høglend et al. 2006).

In the lengthy mid-phase of treatment, the sessions may take on a ritualized format. The patient tells stories in fine detail that he or she believes factually necessary to complete, while affect is largely isolated and compartmentalized. The patient may speak in a monotone, offering few indications of affect. Although the patient may wish for some degree of emotional closeness and engagement with the therapist, the patient resists anything giving rise to discomfort, even in minor degrees, and thus effectively shuts out the therapist. The same memories or events are reiterated in session after session, with the addition of detail, explanation, expansion, and revision but without emotional experience.

When the therapist notes evidence of unconscious processes, such as slips of the tongue, lateness, or withholding of the fee, the patient is likely to dismiss such observations as insignificant. The patient may acknowledge them as possibly meaningful only after rationalization, intellectualization, or undoing leaves little of emotional meaning to work with. Superficially compliant at times, patients with OCPD are prone to remain secretly resistant to accepting insights and integrating them. Sometimes, they characterize and distort what the therapist says so that the therapist appears ridiculous, thereby positioning the patient as an omniscient critic.

To avoid the anxiety that discussion of parapraxes (e.g., a slip of the tongue) arouses, such patients may watch what they say very carefully, trying to avoid spontaneity. If they report dreams, the dreams are likely to be obscure and baroque in detail. Sometimes, the therapy session will be flooded with so much detailed dream material that the therapist is left struggling to find anything that makes emotional sense. The patient ritualizes the therapeutic encounter and is likely to fence the therapist in by never coming late, paying the fee immediately, and becoming superficially very "good" in the service of keeping problems out of the treatment. Occasional lateness, the odd spontaneous remark that seems nonsensical, or a short delay in paying the fee is a welcome opportunity for exploration that can deepen understanding.

Therapists must patiently point out the various manifestations of character defenses, especially the ritualization of the exchange in the service of controlling it while minimizing anxiety. Patients must be shown how their need to get each statement exactly right, to neutralize, to control, and to withhold represents an unconscious effort to overpower the therapist and to make him or her ineffectual. They must learn to increase their tolerance for anxiety within the context of reducing their fear of the therapist, who in time may be experienced more and more as a potential source of criticism—a stand-in for their internalized severe superego. As the therapeutic alliance builds, the patient slowly recognizes that increased anxiety tolerance allows greater emotional elaboration and exploration. Opening up psychologically, setting aside the need to control and to be right, must come to be seen as desirable and not something to be feared and automatically avoided.

Psychodynamic psychotherapy for OCPD organizes itself around three basic considerations: 1) attention to the typical defenses, 2) softening and modification of severe conscience or superego attitudes, and 3) identification and working through of underlying unconscious conflicts and relationship patterns that gen-

erate the patient's complaints, especially as they manifest in developing resistance and transference. Addressing defenses can begin early on, whereas addressing superego concerns, unconscious conflict, and transference requires a more developed alliance with the patient.

When working with the typical defenses of patients, the therapist should keep in mind the hierarchy of adaptation. Obsessional defenses such as isolation, intellectualization, and undoing allow important ideas, even conflicting ideas, into the session but at the expense of keeping affective experience out. Displacement brings in real issues but keeps attention away from the patient. Reaction formation turns real feeling into its opposite (e.g., anger into concern) but still hints at the original underlying feeling. Rationalization disguises or covers up the patient's motivational life. Defenses lower on the hierarchy are more diverting. After these defenses have come into play, the therapist must supportively note and question them so that the patient can see how the defenses help him or her avoid anxiety at a price of emotional constriction. Defense interpretation is most successful when the therapist focuses on defensive actions that the patient can identify and for which a new defense higher on the hierarchy is readily substituted—for example, self-observation (including emotional awareness) for intellectualization or self-assertion for displacement (Perry and Bond 2005). High adaptive-level defenses promote self-awareness and a freer, less constricted life, thereby replacing a controlling, rigid style that hurts personal relationships and work performance. Substantial change in defensive functioning may take years (Perry and Bond 2012).

Patients with OCPD are particularly inclined to believe that the direct expression of affect invites extreme overreaction in others (including the therapist)—that to think something or to feel an impulse to act in some way is little different from acting on it. They are prone to magical thinking in this sense. An erotic thought or angry impulse is likely to be checked immediately as a possible occasion for punishment from outside. It will certainly be punished by one's own severe and rigid conscience or superego. Thus, not only thoughts and feelings that rise to consciousness but also fantasies and impulses are kept out of awareness by defensive operations.

For this reason, patients react fearfully to affectively colored material—whether hostile or erotic—that arises in the transference, and they automatically tend to distance themselves from it through intellectualization, reaction formation, or rationalization. For example, a patient may protest that he or she feels no hostility toward the therapist, even when something obviously hostile occurs during the session, such as challenging the therapist as to why the patient is not better yet.

As attention to the controlling defenses proceeds, anxiety will rise, and the patient's harsh superego attitudes will be projected in the transference. Increased affect tolerance and expression will allow hostile, controlling, and even sadistic wishes to arise. The themes of punishing and retaliation may emerge as leading concerns. As the patient becomes increasingly aware of his or her need to control the treatment (to torment, devalue, even dirty the therapist and his or her efforts) and to resist the free flow of associations, the patient will experience the therapist, at least in part, as a watchful, hostile person who may retaliate in kind. If the therapist carefully avoids enacting this patterned role and interprets what is going on, most patients with OCPD will moderate this

negative, frightening view of the therapist and come to appreciate that this negative transferential attitude forms a major resistance to progress.

As the therapist explores and interprets the transference, the therapist should support the patient's growing ability to observe his or her own psychological experience and processes (self-observation). Appropriate self-revelation can add to reality testing of the negative transference, with close attention to the distortions that support it. This enables the patient to understand the extent of his or her guilt and to grasp the unconscious need to be punished for what the patient experiences as the "badness" of his or her own wishes, especially aggressive impulses. As inhibitions are addressed, more meaningful wishes can emerge for exploration.

As the patient recognizes that hostile or erotic wishes are not the same as acts and sees that the utterance of such material does not require moral condemnation, anxiety should diminish. In experiencing the therapist's kindly, interested acceptance of the entire range of the patient's affects and fantasies, critical superego attitudes soften. Experiencing understanding by the therapist allows the patient to substitute a benevolent attitude of self-awareness for harsh, unrealistic self-judgment. Depression is likely to lift as a consequence, and masochistic behavior that invites suffering can diminish. This development allows a relaxation of defenses against hitherto warded-off fantasies and feelings, enrichment of the therapeutic exchange, and strengthening of the therapeutic alliance.

As therapy progresses, the patient will modify self-expectations and take an interest in and nonjudgmental attitude toward the flow of feelings and thoughts: mindfulness in lieu of the former continuous state of constriction. The patient recognizes that he or she can pick and choose among the various possibilities for action when freed from the constraining belief that every thought and feeling must be assigned a moral value. The patient learns about, and has a chance to modify, the depth and reach of his or her conscience or ideals that heretofore demanded an impossibly clean, polite, and orderly mental life. Omnipotent expectations for perfection of performance and achievement diminish in the course of this work. Relationships are likely to improve, and greater flexibility at work follows, with greater ease in cooperation and less compulsive devotion to work, thereby opening the door to the achievement of a wider range of realistic goals. With enhanced ability to choose, income may also improve.

Cognitive-Behavioral Therapy

A.T. Beck et al. (2004) and J.S. Beck (1997) have devised CBT for personality disorders based on the assumption that specific personality disorders reflect views of the self and others emanating from core beliefs and related maladaptive strategies. To foster the alliance, some patients need to begin a session by telling whatever is on their mind; otherwise, they may resist the therapist's directing them to more structured tasks. The therapist formulates the case and then chooses techniques to foster accurate self-appraisal and independent decision making and behavior. While initially accepting the patient's behavior, the therapist encourages self-reflection and agenda setting of goals and priorities for sessions, often using a homework sheet (e.g., the Dysfunctional Thought Record) to record problems between sessions.

A.T. Beck et al. (2004, pp. 77–78) listed 10 techniques that they apply as needed: 1) using guided discovery, 2) searching for idiosyncratic meaning, 3) labeling inaccurate inferences or distortions, 4) collaborating with the patient to test the validity of his or her beliefs, 5) using interpretations and expectations, 6) examining explanations for others' behavior, 7) scaling patient interpretations to translate dichotomous thinking into finer distinctions, 8) deliberately exaggerating an idea to evaluate its dysfunctional implications, 9) examining the advantages and disadvantages of maintaining versus changing beliefs and behaviors while clarifying their primary and secondary gains, and 10) decatastrophizing, countering the tendency to focus on the worst possible outcomes of a situation.

J.S. Beck (1997) recommended a session format that includes checking the patient's mood, providing a bridge between sessions, setting an agenda for the session, reviewing any homework, discussing the items on the agenda, and then summarizing the session and giving and obtaining feedback. The formulation or "cognitive profile" helps the patient understand connections among early experiences, core beliefs, and compensatory strategies, as well as reactions to current situations. Once therapist and patient have identified maladaptive core beliefs, the patient can fill out a "core belief worksheet" each session, contrasting the old maladaptive belief with disconfirming experiences and substituting new, more flexible and adaptive beliefs. The therapist can help the patient discover and shape new ways of thinking and behaving, such as proposing a behavioral experiment to test a belief. Increasing experience with personality disorders has led authors to note specific problems affecting treatment, including problems with the therapist's reactions to them (J.S. Beck 2005). Brown et al. (2004) found that CBT reduced self-reported dysfunctional beliefs in personality disorders, but it is not yet demonstrated whether this is the primary mediator of other changes.

Schema-focused therapy (SFT) is a variant of CBT that focuses on deeper schemas that organize core beliefs and related modes of behavior, coping, and automatic thoughts. Young et al. (2003) began by identifying which of 18 schemas underlie patients' maladaptive cognitions and coping. These are divided into five major domains: 1) disconnection and rejection (e.g., abandonment/instability, emotional deprivation, defectiveness/shame); 2) impaired autonomy and performance (e.g., dependence/incompetence, failure); 3) impaired limits (e.g., insufficient self-control/self-discipline); 4) other-directedness (e.g., subjugation of needs and emotions, approval seeking, recognition seeking); and 5) overvigilance and inhibition (e.g., emotional inhibition, unrelenting standards and hypercriticalness). The therapist identifies which of four modes—child, maladaptive coping, dysfunctional parent, and healthy adult—the patient is experiencing and operating in. Compared with healthier persons, patients with personality disorders require more attention to modes to help the patients to gain awareness of problematic thinking and behavior—making it ego-dystonic—reflecting the underlying schema. SFT has some resemblance to dynamic therapy: exploration of the past and making connections with present patterns, encouraging emotional processing and insight, and attending to transference and countertransference issues, although SFT is more active and directive (Young et al. 2003).

CBT has begun to examine the phenomenon of resistance to treatment, a staple in dynamic approaches. Young (1999) noted that factors of schema mainte-

nance, such as being in a relationship with a domineering individual, and schema avoidance (of affects, behaviors, or cognitions) allow the patient to avoid experiencing and therefore dealing with maladaptive schemas and schema overcompensation. The therapist must direct the patient's attention to what is avoided, sometimes using the countertransference reaction as a clue (Leahy 2001). Specific SFT approaches to individual Cluster C personality disorder types have not yet been developed.

Avoidant Personality Disorder

Several studies have employed CBT approaches to the treatment of AvPD (Alden 1989; Emmelkamp et al. 2006; Stravynski et al. 1982); others have examined whether AvPD is a predictor of treatment response in major depression (Barber and Muenz 1996) or social phobia (Mersch et al. 1995). All studies showed positive results. Stravynski et al. (1982) compared social skills training with and without cognitive modification, both following somewhat more behavioral models. Social skills training involved instructions about social targets, modeling, role rehearsal, feedback, self-monitoring, and homework. Both individual and group formats were used, and target behaviors were practiced until deemed satisfactory. Cognitive modification involved analyzing, in the session, sequences involving distressing events, irrational beliefs, and their consequences and a process of disputing and planning subsequent new courses of actions. Homework was also used. Significant change occurred in target behaviors, and anxiety decreased, but no advantage was obtained by the combined approaches over social skills training alone.

Emmelkamp et al. (2006) compared cognitively oriented CBT with dynamic psychotherapy and wait-list control conditions in a format of 20 individual sessions over 6 months. CBT techniques included Socratic dialogue, monitoring of beliefs, analyzing advantages and disadvantages of avoidance, activity monitoring and scheduling, graded exposure assignments, behavioral experiments, and role-play. Both treatments were better than the waitlist control condition for most measures, but CBT demonstrated greater change in several measures tied to personality beliefs, which measures by design favored CBT. However, a longer comparative treatment trial of 40 sessions of CBT and dynamic therapy for patients with Cluster C disorders (62% with AvPD) found that the two treatments had comparable trajectories of improvement to 2-year follow-up (Svartberg et al. 2004).

Barber and Muenz (1996) found that among patients treated for major depression in TDCRP, those with AvPD and avoidant traits showed somewhat better outcomes with CBT than IPT. The structured approach of CBT fostered a more rapid response to treatment. The longer study of Svartberg et al. (2004) suggests that this differential response may be limited to treatments of short duration.

Treatment gains may not be impressive immediately after a period of therapy but may become more evident after a longer period of exposure to avoidant situations. This reflects delayed treatment effects in the patient who has taken to continuing to push against avoiding situations that he or she only began to master in therapy. Follow-up data indicate that some patients maintain gains or even improve on some measures several months to years after completing the treatment course (Heimberg 1996; Mersch et al. 1991). However, in one long-term follow-up, patients with AvPD continued to improve more slowly than those

with other types of personality disorders (Kvarstein and Karterud 2012). For patients with more severe personality disorders, additional treatment is indicated after a brief treatment course (Kvarstein and Karterud 2012; Mersch et al. 1991). Despite finding significant improvements in treatment targets, Stravynski et al. (1982) noted the lack of generalization to actual intimate relationships at a 6-month follow-up and suggested the need for some form of intimacy training. Some believe that such patients may benefit from a subsequent course of psychodynamic therapy or IPT.

The cognitions of the patient will affect that patient's assessment of any exposure experience and will determine whether the exposure is desensitizing or whether it paradoxically may be an experience that further reinforces negative cognitions. This is one interpretation of those studies in which long-term follow-up indicated relapse after exposure therapy alone but maintenance and enhancement of gains after CBT. The goal of CBT should be to alter the patient's self-critical cognitions and expectations of critical assessment by others and to challenge the common belief that any unpleasant emotion or interaction is intolerable. However, it is important to avoid an intellectual struggle with the patient and to consider any other beliefs that may underlie what is often seen as treatment resistance. If the patient's tendency to negatively interpret social interactions has been addressed in therapy, then the exposure experiences can positively alter the patient's overall assessment of his or her experience in the world.

Dependent Personality Disorder

A.T. Beck et al. (2004) and J.S. Beck (1997) have described CBT for DPD. Although autonomy and the ability to develop close relationships are overriding aims, the therapist first encourages the patient to set goals for treatment to encourage collaborative working. For instance, the therapist should encourage the patient to start the session, choosing what to talk about rather than leaving it up to the therapist (A.T. Beck et al. 2004). By using a Socratic method, the therapist avoids directing the patient's agenda. Using guided questioning, the therapist continually challenges the patient's dichotomous thinking (e.g., "If I am not fully successful, then I'm inadequate") to improve self-evaluation. Successful graded exposure to anxiety-provoking situations in real life challenges the patient's belief about being incompetent. Patient diaries can be used to monitor the patient's automatic thoughts, especially of inadequacy, highlighting their negative consequences. The therapist challenges the patient to select healthier responses that help develop positive schemas. Relaxation training may aid in the reduction of anxiety surrounding independent reflection and decision making. Assertiveness training and role-playing may help counter submissive behavior whenever real skill deficits exist.

Whenever resistance to change develops, the therapist must help the patient confront ambivalence about changing, with the goal of finding constructive substitutes for the loss of old dependent habits. As treatment progresses, the dependent transference can be reduced by the addition of group therapy. In other cases, exploration of dependent issues as they occur in the patient-therapist relationship can have a strong effect (A.T. Beck et al. 2004). Toward termination, tapering the frequency of sessions will allow the patient to feel increasingly competent without frequent visits. At termination, the patient's fear of losing the therapist may be mitigated by the offer of booster sessions

at infrequent intervals. Specific guidelines regarding the optimal number of sessions have not yet been developed or tested.

In a retrospective study of CBT for panic disorder with agoraphobia, Marchand and Wapler (1993) found that a chart diagnosis of DPD (vs. those without DPD) was not associated with worse treatment response. The clinical consensus is that CBT is often effective in DPD.

Obsessive-Compulsive Personality Disorder

In the TDCRP, Barber and Muenz (1996) found that depressed patients with OCPD and OCPD traits responded better to IPT than to CBT. It is possible that the emphasis on maladaptive cognition tends to obscure the development of a fuller affective experience in therapy and also to stimulate the patient's rigidity, stubbornness, and belief that he or she is more correct than the therapist. Studies of CBT for the symptom disorder—that is, obsessive-compulsive disorder—do not generalize to OCPD, however, because the symptoms are ego-syntonic. Although the findings of Svartberg et al. (2004) that CBT and dynamic therapy of less than 1 year's duration were equally helpful for Cluster C personality disorders (including OCPD), the lack of studies of long-term treatment leaves little empirical basis to recommend long-term CBT for OCPD absent further study.

Other Individual Therapies

Supportive Therapy

Supportive therapy has been applied to Cluster C personality disorders in a short-term individual format (Rosenthal et al. 1999). Although the therapy was effective, the reported effects for the Inventory of Interpersonal Problems were on the low side: effect size was 0.52 versus 0.91 for the mean of six studies (Perry and Sanlian 2002). Longer treatment durations have not been studied. The aim of supportive therapy is to use the therapeutic relationship to help the patient draw on capabilities already available to deal with his or her problems. The therapist emphasizes a good listening relationship, respect, and empathy, relying on so-called supportive techniques such as acknowledgment, questions, reflection, clarification, and direct suggestions and even praise. These allow the patient to reconstitute from crises and address issues using his or her own best resources available. As such, the goals have generally not been to foster extensive changes in personality functioning, but may be highly appropriate in times of crisis. It is yet unknown whether individual types of personality disorders have a differential response to supportive therapy over longer durations.

Interpersonal Therapy

IPT originated as a treatment for the interpersonal issues related to depression. Some studies examined the effects of IPT on largely Cluster C personality disorders as an acute (Hardy et al. 1995; Shea et al. 1990) or maintenance treatment (Cyranowski et al. 2004). Although IPT is effective in targeting depressive symptoms, in an 8-week format IPT may not be as effective as CBT, whereas in a 12-week format the two treatments may be equal (Hardy et al. 1995). Shea et al. (1990) found that 16 weeks of IPT did not lead to recovery of depression in personality disorders as often as it did in other psychiatric disorders. Adaptations of IPT specifically targeting the interpersonal problems of Cluster C personality disorders would be a promising development. IPT is commonly done in a short-term format, such as 16 sessions, and focuses on relationships in the patient's outside life, generally not including the transference. Longer-term formats, other than

maintenance treatment for depression, would be informative.

Transference-Countertransference Issues

Tables 73–1, 73–2, and 73–3 display the common transference-countertransference patterns that may arise in the treatment of each of the three personality disorders, across any treatment type. Each reflects the potential effects on the therapist of the patient's way of relating. Given these emotional responses, to avoid acting defensively (so-called "defense enactments"), the therapist must be aware both of what the patient is doing and of the therapist's own normal and neurotic reactions. Successful exploration with the patient can foster insight applicable to other relationships outside of therapy as well.

TABLE 73–1. Transference and countertransference patterns: patients with avoidant personality disorder

Transference	Countertransference
The patient's sensitivity to criticism by self or others leads him or her to avoid significant topics that precipitate the associated feelings of shame and diminished self-esteem.	The therapist is hesitant to say anything that might be experienced negatively, thereby avoiding issues that underlie the problem in self-esteem regulation.
The patient continually presents his or her failings in the hope of eliciting positive comments to boost self-esteem.	The therapist assumes a positive supportive role, feeling that the patient has not received enough praise. The patient's avoidance defenses and behaviors are left unchallenged.
The patient idealizes the therapist and basks in the reflected esteem he or she attributes to the therapist.	The therapist accepts the idealized role, failing to attend to the patient's negative experiences in the transference. The patient makes the therapist the main intimate relationship and, while avoiding the negative transference, fails to address conflicts with others that would allow him or her to develop other relationships.

Other Therapeutic Modalities

Group Psychotherapy

The group therapy literature usually treats Cluster C personality disorders together, and often includes other personality disorder types as well (Budman et al. 1996). In general, group therapy has been found effective as a sole modality (Alden 1989; Budman et al. 1996), but it is also used as a major component in day treatment programs (Krawitz 1997; Kvarstein and Karterud 2012; Piper et al.

TABLE 73–2. Transference and countertransference patterns: patients with dependent personality disorder

Transference	Countertransference
The patient makes many requests for help and guidance early in treatment.	The therapist withdraws from the patient, increasing the risk for early termination.
The patient idealizes the therapist as all-knowledgeable and gives him or her responsibility for important decisions.	The therapist assumes a directive role because of frustration with the patient or a wish to be idealized.
Because of a wish to preserve the attachment to the therapist, the patient fails to advance.	Because the patient is overtly cooperative, the therapist fails to confront the lack of real change.
The patient is unable to leave a repeatedly abusive relationship, evoking in the therapist the desire to control or punish the patient.	The therapist experiences frustration and pushes the patient to leave the abusive relationship. The patient feels threatened, and separation anxiety increases.
The patient avoids dealing with separation, loss, and disappointment issues, including mourning. The patient avoids facing the eventual loss of the therapist in advance of termination.	The therapist colludes with the patient due to a fantasy of always being available for the patient. The patient may be reluctant to make changes by accepting loss and gaining independence.

1993; Soeteman et al. 2011; Wilberg et al. 1998) and as an adjunct to outpatient individual therapy. Group therapy for Cluster C disorders is effective, with studies finding an average median effect size for active treatments across all measures of 0.9 at termination and 1.1 at follow-up (Alden 1989; Ball et al. 2000; Budman et al. 1996; Krawitz 1997). Improvement has been shown in general areas such as distress, depression, and global and interpersonal functioning, although some studies have shown improvement in disorder-specific symptoms such as shyness or social avoidance (Alden 1989). Sizable improvement or recovery following group therapy as a sole modality is not common (Budman et al. 1996), but is more common when treatment durations continue beyond 6–12 months (Wilberg et al. 2003), although longer treatment durations are rarely studied.

Avoidant Personality Disorder

Alden (1989) devised three CBT approaches for AvPD given over 10 weeks in group therapy sessions lasting about 2.5 hours each. Patients in all three groups worked to establish goals for between-session work, including identifying fears related to avoidance, increasing awareness of anxiety related to dwelling on the fears, and shifting attentional focus from fear to actions. The graduated exposure group identified a hierarchy of feared interpersonal situations and, after discussion and practice in the group, tried social tasks outside the group, beginning with easier and moving toward harder tasks. The interpersonal skills training group received progressive relaxation training followed by training in four sets of skills: listening/attending skills, empathic sensitivity, appropriate self-disclosure, and respectful

TABLE 73–3. Transference and countertransference patterns: patients with obsessive-compulsive personality disorder

Transference	Countertransference
The patient avoids his or her sensitivity to criticism through rigidity of thinking. The patient reiterates the correct way of thinking or doing things and avoids emotional exploration.	In response to the therapist's attempts to challenge the patient's rigidity, the patient criticizes the therapist, who feels angry and powerless to affect the patient. The therapist ceases to challenge the patient's rigidity for fear of provoking an endless debate. A therapeutic stalemate ensues.
The patient prefers turning vignettes into intellectual discussions about himself or herself or people in general. This keeps anxiety at bay but minimizes felt emotions.	The therapist is tempted to trade point for point, and interpretations become intellectualizations that have no mutative power.
The patient uses isolation of affect in describing important stories. He or she gives a litany of lifeless details, thereby avoiding deeper experiences and their related meanings.	The therapist is bored, gets sleepy, or retreats into daydreams. Interestingly, the daydreams may connect in some way to the patient's affect that is being avoided.
The patient projects a critical attitude onto the therapist and then responds to that.	Feeling unjustly accused, the therapist becomes annoyed so that subsequent remarks sound defensive or critical, thereby reinforcing the patient's expectations.

assertiveness. Outside practice was encouraged. The intimacy-focused group received both graduated exposure and interpersonal skills training but with a greater emphasis on using skills to develop more intimate relationships. All three treatments were efficacious compared with a wait-list control condition and were largely equal in effect, although there was some indication that patients in the intimacy-focused group reported greater frequency of engagement in and satisfaction with social activities at termination or follow-up. Nonetheless, the time frame was insufficient for producing full recovery compared with normative standards for the measures.

Dependent Personality Disorder

Group psychotherapy can be successful for DPD. In a study of group therapy for patients who used medications for chronic complaints such as insomnia and nervousness, Montgomery (1971) reported that 90% of patients eventually discontinued medications and began to confront their anger at being dependent on the therapist. In an inpatient treatment setting for alcoholism, Poldrugo and Forti (1988) found group therapy more beneficial for patients with DPD than for those with other personality disorders. Sadoff and Collins (1968) employed weekly group

psychotherapy for patients who stuttered, most of whom had passive-dependent traits. Although attrition was high, the authors found that the interpretation of passive-dependent behavior and attitudes (e.g., asking for help, believing that others are responsible for helping them) as a defense against recognizing and expressing anger proved helpful. Both stuttering and passive dependency improved in two patients who became angry and were able to confront their anger. Torgersen (1980) studied college students attending a weekend-long encounter group. On follow-up several weeks later, individuals who initially scored high on dependent traits had mixed responses. Although the group experience left them feeling disturbed and anxious, they also reported becoming more accepting of their own feelings and opinions.

Attrition may be higher in group than individual therapy for personality disorders (Perry and Bond 2000), although it may be less of a problem for patients with Cluster C disorders, particularly DPD, or for those participating in group therapy offered in the context of partial hospitalization. Budman et al. (1996) noted moderate improvements after an 18-month group therapy for outpatients with personality disorders, with the beginning of change not evident until 6 months into treatment. Most clinicians employ weekly sessions lasting 1–1.5 hours. Whenever group therapy is the major treatment modality in a day or residential treatment setting, session frequency may be higher (Krawitz 1997; Piper et al. 1993; Wilberg et al. 1998). Outpatient group therapy generally lasts 6 months to several years.

Obsessive-Compulsive Personality Disorder

Some authors have reported a favorable response for patients with OCPD treated in a group setting (Schwartz 1972). Confrontation of the patient's defenses may be more effective in group than in individual treatment settings (Wells et al. 1990). Issues that can be confronted in the group setting include modification of cognitive style, assistance with decision making, modification of harsh attitudes, increased comfort with emotional needs, increasing comfort with affective experience, resolution of control issues, and modification of interpersonal style. Advantages of group therapy include a diffusion of power among group members, which lessens the potential for the "tug-of-war" that is common in individual treatment, as well as an opportunity to develop trust in a number of group members. Group consensus and peer pressure may lessen resistance. The emphasis on here-and-now interaction among group members brings conflicts to life. The therapeutic process within the group, with its potential for alternating roles, helps to increase patient flexibility.

Family Therapy

Some patients live with family members who exert great degrees of influence over issues of support and autonomy. The family may view the patient as needing to be cared for, directed, or corrected, and the family reward and punishment contingencies may maintain the patient in a dependent status. Increasing autonomy by the patient, such as a threat of leaving home or a pattern of resisting pressure to change, is covertly experienced as threatening to the family. In such cases, family therapy or periodic family meetings adjunctive to individual therapy may help. The therapist's first task is to identify the functional relationships in the family that encourage dependency and discourage normal autonomy. The therapist must then help the family members develop a consensus on some modest goals for in-

creased autonomy for the patient. The hardest part may be to get the patient and family to "buy in" to working toward consensual goals. As the patient begins to reach some early goals, the therapist can help the family revise the consensus. The therapist must point out discrepancies between attitudes of helping the patient and behaviors that undermine this goal. However, the alliance with the family members may become strained if the therapist takes too directive a stance. Family meetings range from once per week to once every few months when adjunctive to individual or residential therapy. There are no studies on the sole use of family therapy for Cluster C personality disorders. Whether there is a subpopulation, such as late adolescents, for whom this might be effective as a sole treatment is unknown.

Day and Residential Treatment

Both day and residential treatment modalities are useful when patients require a higher level of support, treatment intensity, and variety than is available in most outpatient therapies. Patients usually have comorbid symptom and personality disorders and a history of refractoriness to previous treatments (Karterud et al. 1992, 2003; Piper et al. 1993; Wilberg et al. 1998), including repeated inpatient stays. Such programs usually employ mixtures of individual and group therapies along with additional services, such as occupational therapy, expressive therapies (e.g., art, exercise, psychodrama), guided work experiences or counseling, and so forth. Controlled (Piper et al. 1993) and uncontrolled (Karterud et al. 1992, 2003; Krawitz 1997; Wilberg et al. 1998) studies including Cluster C personality disorders generally demonstrate large effects (in the range of 0.8–2.1). The large Dutch Study on Cost-Effectiveness of Personality Disorder Treatment found that day hospital or inpatient psychotherapy programs that were short term (less than 6 months) were the most cost-effective for Cluster C personality disorders in terms of producing an additional quality-adjusted life year compared with long-term inpatient or short- or long-term outpatient psychotherapy (Soeteman et al. 2011). Treatment assignment was not random. Short-term, intensive treatments appear to be effective at favorable costs.

Temple et al. (1997) found that interpretive group therapy was specifically helpful, enabling most of a group of patients who were very dependent on day hospital treatment to improve enough for discharge to outpatient care. The duration of day treatment programs ranges from about 18 weeks to more than 1 year, although a naturalistic comparison of different day treatment centers in Norway found no differences in effectiveness for personality disorders between longer and shorter treatment durations (Karterud et al. 2003). However, there may be subpopulations of patients, such as those with childhood histories of emotional neglect or sexual abuse, who require longer durations and do not show improvement until later in their treatment course. Residential treatment is specifically useful for those patients who have failed to improve or have deteriorated with outpatient therapy or while living alone or with family, or for those for whom serious suicidality is a problem. Such patients usually require several months to a year or longer to progress to the point of living independently and benefiting from outpatient therapy.

Biological Treatments

Most pharmacological studies have examined whether the presence of a Cluster C diagnosis affects treatment response

for symptom disorders. Shea et al. (1990) found that patients with major depressive disorder who also had Cluster C personality disorders showed significant improvement in depression with imipramine, CBT, or IPT. However, such patients had higher levels of symptoms and impairment at baseline and at the end of 16 weeks of treatment and follow-up compared with the patients who did not have personality disorders. Also, fewer patients with Cluster C personality disorders than patients without personality disorders attained full recovery from depression (30% vs. 49%). Hardy et al. (1995) replicated these findings for CBT and dynamic IPT, comparing patients with depression who did or did not also have Cluster C personality disorder after 8 or 16 weeks of psychotherapy. Kool et al. (2003b) found that combined medication and psychotherapy was superior to medication alone in personality disorder patients with major depression, producing remission in 46.9% (vs. 19.4% for medication alone) at 24 weeks.

Avoidant Personality Disorder

Currently, there is no systematic evidence supporting pharmacotherapy as a primary treatment modality for AvPD per se. Most research has been directed to the treatment of patients with depression and specific and generalized social phobia who may also have AvPD.

A number of medications have been found effective in patients with generalized social phobia, a frequent concomitant in AvPD. In a sample of persons with generalized social phobia, about half of whom had AvPD, the monoamine oxidase inhibitor (MAOI) phenelzine was effective by 8 weeks and remained so at 16 weeks, compared with the β-blocker atenolol or placebo (Liebowitz et al. 1992). Phenelzine led to decreased anxiety and social avoidance and some decrease in avoidant personality features. Selected anxiolytics have been found efficacious, such as the moderately long-acting benzodiazepine clonazepam, which may also be associated with less difficulty in withdrawal after months of treatment (Connor et al. 1998). Allgulander (1999) found that the selective serotonin reuptake inhibitor (SSRI) paroxetine ameliorated the symptoms of social phobia. MAOIs, SSRIs, and venlafaxine may affect some of the core dimensional features of AvPD, such as shyness, rejection sensitivity, and heightened psychic pain, that reinforce distorted cognitions related to self-criticism and self-effacement, probably by mitigating the rapid and pronounced affective response to social stressors, but this remains to be demonstrated. Following any symptom amelioration, however, the patient still must confront areas heretofore avoided. Consistent with this, Kool et al. (2003a) found that avoidant traits in depressed subjects improved more with combined medications and psychotherapy than with pharmacotherapy alone.

Dependent Personality Disorder

Klein et al. (1973) found that imipramine was no more effective than placebo in hospitalized patients with passive-aggressive and passive-dependent personality disorders. Lauer (1976) gave tricyclic antidepressants to patients with passive-dependent traits in addition to their primary diagnoses. On follow-up questionnaires, patients reported less anxiety along with increases in available energy, assertiveness, and outgoing behavior, although the results were not very striking. Ekselius and von Knorring (1998) treated depressed patients, 61% of whom scored in the personality disorder range by self-report questionnaire, with sertra-

line or citalopram for 24 weeks. From baseline to termination, the percentage above the cutoff score for DPD improved significantly (21% vs. 8%), as did the mean number of DPD criteria met by the whole sample (3.3 vs. 2.3), even after controlling for change in observer-rated depression. Although the comparison across two different measurement perspectives complicates these findings, self-reported dependent symptoms seem to improve with 24 weeks of SSRI treatment. In depressed patients, Kool et al. (2003a) found that combined psychotherapy and medications improved self-reported DPD symptoms more than pharmacotherapy alone. Fahlén (1995) examined changes in dependent traits among individuals with social phobia recruited for a 12-week randomized controlled trial of brofaromine, a monoamine oxidase A inhibitor with serotonin-inhibiting properties. Compared with placebo, the drug yielded a significant decrease in the number of avoidant and dependent criteria present, as scored by the clinician. On self-report, patients taking the drug reported a decrease in indecisiveness and risk avoidance. Anecdotally, the author reported a rise in self-esteem among drug responders.

Overall, pharmacotherapy in patients with DPD may improve symptoms of concurrent depression, but full recovery in these patients is less likely than in those without personality disorder. Although the idea is popular and short-term studies are suggestive, there is little evidence of sustained, long-term benefits in personality functioning from pharmacotherapy.

Obsessive-Compulsive Personality Disorder

No medications specific for the treatment of OCPD are currently available. The serotonin reuptake inhibitors used in the treatment of obsessive-compulsive disorder (OCD) have not been carefully studied in OCPD. Anecdotal reports (Stein and Hollander 1993) of the efficacy of these medications in patients with OCPD have not been confirmed by controlled studies. Nonspecific anxiolytic agents may be used, but only for short periods of time (days to weeks) to avoid the potential of medication dependency. Swartz (1998) reported that the long-acting β-adrenergic blocker betaxolol was useful for anxiety in patients with OCPD. When depressed, patients with OCPD may respond to antidepressants, with some amelioration of the symptoms of OCPD (Ekselius and von Knorring 1998), but Kool et al. (2003a) did not find this to occur. Pollitt and Tyrer (1992) found that compulsive personality disorder was a positive predictor of response to serotonergic antidepressants.

Conclusion

The evidence is overwhelmingly consistent that individual psychotherapies, including dynamic and cognitive or CBT types—with fewer data for IPT and supportive types—are efficacious and effective in producing improvement in Cluster C personality disorders. For individuals with greater degrees of impairment in social and occupational functioning, often accompanied by greater comorbidity of symptom disorders, the evidence is less plentiful but highly consistent that partial or day hospital programs or residential programs, both short-term and those lasting 6 months or longer, lead to significant improvement. Studies usually have not produced sustained recovery on most measures employed. However, in the time frames studied, Cluster C disorders are more likely to recover from full criterion personality disorder status than is true for

Cluster B disorders. These findings in the context of limited treatment and follow-up durations—usually 1 year or less—suggest the need for treatment to continue longer than 1 year in the majority of cases. Short-term therapies may ameliorate symptoms, but they do not produce sustained recovery in most individuals.

The evidence is less robust for pharmacological treatments. To date, there is little reason to target the personality disorder itself, apart from treating comorbid symptom disorders. Patients with personality disorder often have higher levels of symptoms at the start or respond less consistently early on and may respond better to combined medications and psychotherapy than medications alone. Further study is needed to show whether combined treatment will lead to lower risk for relapse or recurrence compared with either medications or psychotherapy alone.

Patients, families, mental health professionals, and third-party payers should consider the likelihood of improvement against cost, when it is theirs to bear. All should weigh the benefits of more intensive or longer-term treatments aimed at producing sustained recovery versus those of amelioration, shy of full recovery, which is produced by the majority of short-term therapy or pharmacological approaches alone. What is less costly in the short term is not likely to be more cost-effective in the long term whenever impairment versus healthy functioning is measured over the life span. Rather, far lower levels of distress and impairment are likely to be proven both personally desirable and cost-effective in the long run. Of all the personality disorders, the Cluster C disorders are the best candidates for attaining healthy functioning if patients are treated for a moderate to long duration.

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