A Guide to

TREATMENTS THAT WORK

FOURTH EDITION

Edited by

PETER E. NATHAN
JACK M. GORMAN

OXFORD

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Fourth Edition

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Preface

In the absence of science, opinion prevails.

Readers familiar with the third edition of *A Guide to Treatments that Work* will notice a number of changes in this edition. First, two chapters have been added to the beginning of the book. Chapter 1, written by the editors, examines in detail two perplexing issues raised by critics of *DSM-5*: (1) the unrealized potential to date of neuroscience biomarkers that would yield more accurate and reliable diagnoses and (2) the continuing burden of overdiagnosis for clinicians and patients alike. Both issues have obvious relevance to treatment. Chapter 2, written by R. Dale Walker, M.D., professor of psychiatry at the Oregon Health & Science University (OHSU), director of OHSU's One Sky Center, and a member of the Cherokee Tribe of Oklahoma, and Douglas A. Bigelow, a long-time colleague of Walker's at OHSU, contrast Native American and Western ways of identifying effective treatments for mental and physical disorders, concluding that "evidence-informed culture-based" interventions sometimes constitute best practices in Native communities.

Two new chapters detailing pharmacological treatments for pediatric bipolar disorder (Chapter 9) and pediatric depressive disorder (Chapter 12), written by Martin, Goldberg, Biernacki, and Rynn of the Department of Psychiatry at Columbia University, have also been added. Both reflect substantial recent advances in diagnosis and pharmacological treatment of these troublesome childhood disorders. A new chapter order reflecting a comparable reordering of chapters in *DSM-5* and ICD-11 has also been implemented. In addition, virtually every treatment review chapter in this edition provides for informed discussion and critical assessment of changes in *DSM-5* from *DSM-IV*.

The goals and standards by which chapter authors evaluated research on treatments remain the same in the fourth edition as they were in the first, second, and third. Like its predecessors, this edition of *Treatments that Work* offers detailed evaluative reviews of current research on treatments for disorders for which evidence-based interventions have been developed. They have been written in most instances by psychiatrists and clinical psychologists who were major contributors to that literature. Many of the chapter authors in this edition also wrote for the first three editions.

The standards by which authors were asked to evaluate the methodological rigor of the treatment research they reviewed have not changed either. Summarized here, as they were in the three previous editions, they are designed to enable authors and readers to assess treatment outcome research in light of the methodological adequacy of the research. Those standards, identical to those that guided chapter authors in the first three editions of this book, are as follows:

> The purpose of these chapters is to present the most rigorous, scientifically based evidence for the efficacy and effectiveness of treatments that is available. At the same time it is clear that for some disorders there are treatments widely

recognized by experienced clinicians to be useful that may not have been subjected to rigorous investigation for a variety of reasons. Our aim is to be clear with readers what treatments are felt by a large number of experts to be valuable but have never been properly scientifically examined, and what treatments are known to be of little value.

To do this, it is useful to establish some criteria for evaluating the validity of articles in the literature that are reviewed in writing the chapters. We would like you to keep in mind the following classification when you are reviewing the literature and writing your chapter:

Type 1 Studies: These are the most rigorous and involve a randomized, prospective, controlled clinical trial. Such studies also must involve comparison groups with random assignment, blinded assessments, clear presentation of exclusion and inclusion criteria, state-of-the-art diagnostic methods, adequate sample size to offer statistical power, and clearly described, appropriate statistical methods.

Type 2 Studies: These are clinical trials in which an intervention is made, but some aspects of the Type 1 study requirement are missing. For example, a trial in which a double-blind cannot be maintained; a trial in which two treatments are compared but the assignment is not randomized; and a trial in which there is a clear but not fatal flaw such as a period of observation that is felt to be too short to make fully valid judgments on treatment efficacy. Such studies clearly do not merit the same consideration as type 1 studies but often make important contributions and generally should not be ignored.

Type 3 Studies: These are clearly methodologically limited. Generally, type 3 studies are open treatment studies aiming at obtaining pilot data. They are highly subject to observer bias and can usually do little more than indicate if a treatment is worth pursuing with a more rigorous design. Also included in this category are case-control studies in which patients are identified and then information about treatment is obtained from them retrospectively. Such studies can, of course, provide a great deal of naturalistic information but are prone to all the problems of uncontrolled data collection and retrospective recall error.

Type 4 Studies: Reviews with secondary data analysis can be useful, especially if the data-analytic techniques are sophisticated. Modern methods of meta-analysis attempt to account for the fact that, for example, negative studies tend to be reported at a substantially lower rate than positive outcome studies.

Type 5 Studies: Reviews without secondary data analysis are helpful to give an impression of the literature but are clearly subject to the writer's opinion and sometimes are highly biased.

Type 6 Studies: This encompasses a variety of reports that have marginal value, such as case studies, essays, and opinion papers.

The editors are pleased to acknowledge the essential contributions of the chapter authors to this volume. We take satisfaction from the fact that more than three quarters of the chapters in this book were written by colleagues who contributed as well to most or all of the previous editions of *Treatments that Work*. We are grateful to all our chapter authors, especially those who have been with us since the first edition.

We would also like to thank the three Oxford University Press editors who worked most closely with us to update this edition. Joan Bossert, Vice President and Editorial Director of Oxford University Press (US), a good friend and superb editor, has worked with us since 1996, when we began to plan the first edition. Sarah Harrington, Psychology Editor at Oxford, has also played an important role in this edition, first by convincing us that we ought to do it, and then by helping us think through some important decisions as we went along. Finally, we would like to acknowledge the efforts of Andrea Zekus, who organized and oversaw the production of the volume to ensure that it met the high standards of earlier editions.

Peter E. Nathan, Ph.D.
Jack M. Gorman, M.D.
September 2014

Contributors

Cindy J. Aaronson, MSW, Ph.D.: Clinical Assistant Professor of Psychiatry, Icahn School of Medicine at Mount Sinai

Atheir I. Abbas, M.D., Ph.D.: Resident in Psychiatry, Department of Psychiatry, College of Physicians and Surgeons, Columbia University

Melissa L. Anderson, Ph.D.: Assistant Professor, Department of Psychiatry, University of Massachusetts School of Medicine

Rebecca L. Ashare, Ph.D.: Assistant Professor, Center for Interdisciplinary Research on Nicotine Addiction, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania

Jacques P. Barber, Ph.D.: Dean, Gordon F. Derner Institute of Advanced Psychological Studies, Adelphi University

David H. Barlow, Ph.D.: Professor of Psychology and Psychiatry, Founder and Director Emeritus, Center for Anxiety and Related Disorders, Boston University

Kate H. Bentley, M.A.: Graduate Student, Transdiagnostic Treatment Lab, Boston University

Carolina Biernacki, M.D.: Pediatric Anxiety and Mood Research Clinic, Columbia University/ New York State Psychiatric Institute

Douglas A. Bigelow, Ph.D.: Professor Emeritus, Department of Psychiatry, Oregon Health & Science University

Daniel M. Blonigen, Ph.D.: Career Development Awardee, Center for Innovation to Implementation, VA Palo Alto Health Care System

Deepa Burman, M.D.: Latterman Family Health Center, University of Pittsburgh Medical Center

Daniel J. Buysse, M.D.: Professor, Department of Psychiatry and Clinical and Translational Science and Director, Neuroscience Clinical and Translational Research Center, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center

Sean Carey, B.A.: Research Coordinator, Child and Adolescent Mood Program, Emory University School of Medicine

Emily Chapman, B.A.: Icahn School of Medicine at Mount Sinai

Laren R. Conklin, Ph.D.: Postdoctoral Research Fellow, Center for Anxiety and Related Disorders, Boston University

Deborah S. Cowley, M.D.: Professor, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine

W. Edward Craighead, Ph.D.: J. Rex Fuqua Professor and Director, Child and Adolescent Mood Disorder Program, Departments of Psychology and Psychiatry & Behavioral Sciences, Emory University

Paul Crits-Christoph, Ph.D.: Professor of Psychology in Psychiatry and Director, Center for Psychotherapy Research, Perelman School of Medicine, University of Pennsylvania

Darin D. Dougherty, M.D.: Associate Professor of Psychiatry and Director, Division of Neurotherapeutics, Harvard Medical School

Boadie W. Dunlop, M.D.: Assistant Professor and Director, Mood and Anxiety Disorders Program, Department of Psychiatry, Emory University School of Medicine

John W. Finney, Ph.D.: Research Health Science Specialist, Center for Innovation to Implementation, VA Palo Alto Health Care System (152MPD)

Maya Genovesi, A.B.: Clinical Research Coordinator/National Coordinator, James J. Peters VAMC (Bronx, NY)

Loren M. Gianini, Ph.D.: Eating Disorders Research Unit, Department of Psychiatry, College of Physicians and Surgeons, Columbia University

Pablo H. Goldberg, M.D.: Medical Director, Childrens' Day Unit, New York State Psychiatric Institute, New York Presbyterian Hospital, Columbia University Medical Center

Julia A. Golier, M.D.: Associate Professor of Psychiatry, Icahn School of Medicine at Mount Sinai; Psychiatry Service, James J. Peters VAMC (Bronx, NY)

Jack M. Gorman, M.D.: CEO and Chief Scientific Officer, Franklin Behavioral Health Consultants

Jon E. Grant, J.D., M.D., M.P.H.: Professor of Psychiatry and Behavioral Neuroscience, School of Medicine, University of Chicago

Laurence L. Greenhill, M.D.: Ruane Professor of Psychiatry and Pediatric Psychopharmacology, Columbia College of Physicians and Surgeons; and Director, New York State Research Unit of Pediatric Psychopharmacology at the New York State Psychiatric Institute

Lauren M. Haack, Ph.D.: Department of Psychiatry, School of Medicine, University of California, San Francisco

Michael A. Jenike, M.D.: Professor of Psychiatry, Harvard Medical School; and Psychiatrist, Massachusetts General Hospital

Benjamin N. Johnson, B.A.: Research Coordinator, Child and Adolescent Mood Program, Emory University School of Medicine

Kyle M. Kampman, M.D. Professor of Psychiatry, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania

Erica Kass, M.D.: NYPH Child and Adolescent Psychiatry Fellow, Department of Psychiatry, Columbia University College of Physicians and Surgeons

Gary Katzman, M.D.: Clinical Assistant Professor, Department of Psychiatry, Icahn School of Medicine at Mt. Sinai

Alan E. Kazdin, Ph.D.: John M. Musser Professor of Psychology and Child Psychiatry and Director, Yale Parenting Center, Department of Psychology, Yale University

Paul E. Keck, Jr., M.D.: The Craig and Francis Lindner Professor of Psychiatry and Neuroscience, Executive Vice Chairman, Department of Psychiatry and President and CEO, the Lindner Center of HOPE, University of Cincinnati College of Medicine

Ryan J. Kimmel, M.D.: Assistant Professor, Department of Psychiatry and Behavioral Science, University of Washington School of Medicine

Henry R. Kranzler, M.D.: Professor of Psychiatry, Director of the Center for Studies of Addiction, Perelman School of Medicine, University of Pennsylvania & VISN 4 MIRECC, Philadelphia VAMC

Matthew M. Kurtz, Ph.D.: Associate Professor of Psychology, Chair, Program in Neuroscience and Behavior, Department of Psychology, Wesleyan University

Daniel Le Grange, Ph.D.: Benioff UCSF Professor in Children's Health, Department of Psychiatry and Department of Pediatrics, University of California, San Francisco

Jeffrey A. Lieberman, M.D.: Lawrence C. Kolb Professor and Chairman, Department of Psychiatry, Columbia University College of Physicians and Surgeons and Director, New York State Psychiatric Institute

Katharine L. Loeb, Ph.D.: Associate Professor, School of Psychology, Director, PhD Program in Clinical Psychology, Fairleigh Dickinson University

Prerna Martin, M.P.H.: Project Manager, Pediatric Anxiety and Mood Research Clinic, Columbia University/New York State Psychiatric Institute

Susan L. McElroy, M.D.: Chief Research Officer, Lindner Center of HOPE and Professor of Psychiatry and Neuroscience, University of Cincinnati College of Medicine

James R. McKay, Ph.D.: Professor of Psychology in Psychiatry, Department of Psychiatry, University of Pennsylvania

Andreas C. Michaelides, Ph.D.: Traumatic Stress Studies Division, Icahn School of Medicine at Mount Sinai; Mental Health Patient Care Center, James J. Peters VAMC (Bronx, NY)

David J. Miklowitz, Ph.D.: Professor, Division of Child and Adolescent Psychiatry, University of California, Los Angeles (UCLA); Semel Institute for Neuroscience and Human Behavior

Rudolf H. Moos, Ph.D.: Emeritus Director, Center for Innovation to Implementation, VA Palo Alto Health Care System (152MPD); and Stanford University School of Medicine

Rachel L. Moster, M.D.: Fellow in Public Psychiatry, Department of Psychiatry, College of Physicians and Surgeons, Columbia University

Anjana Muralidharan, Ph.D.: Post-doctoral Research Fellow, Veterans Affairs Capitol Health Care Network (VISN 5) Mental Illness, Research, Education, and Clinical Center (MIRECC); and University of Maryland School of Medicine

Lisa M. Najavits, Ph.D.: Research Psychologist, Veterans Affairs Boston Healthcare System; and Professor of Psychiatry, Boston University School of Medicine

Peter E. Nathan, Ph.D.: University of Iowa Foundation Distinguished Professor of Psychology and Public Health Emeritus

Charles B. Nemeroff, M.D., Ph.D.: Leonard M. Miller Professor and Chairman, Department of Psychiatry and Behavioral Sciences; and Director, Center on Aging, University of Miami Miller School of Medicine

Pei Huey Nie, M.D.: Assistant Professor, Geriatric Psychiatry Department, VA Greater Los Angeles Healthcare System; and Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA

Brian L. Odlaug, M.P.H.: Visiting Researcher, Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen

M. Mercedes Perez-Rodriguez, M.D., Ph.D.: Assistant Professor of Psychiatry, Icahn School of Medicine at Mount Sinai; and Mental Illness Research Education and Clinical Center, James J. Peters VAMC, Bronx, NY

Linda J. Pfiffner, Ph.D.: Professor of Psychiatry, Department of Psychiatry, University of California, San Francisco

Kathleen M. Pike, Ph.D.: Clinical Professor of Psychology, Departments of Psychiatry and Epidemiology, Executive Director and Scientific Co-Director, Global Mental Health Program at Columbia; and Associate Director, Health and Aging Policy Fellowship, Columbia University

Jonathan E. Posner, M.D.: Assistant Professor, Department of Psychiatry, Columbia University College of Physicians and Surgeons

Marc N. Potenza, M.D.: Professor of Psychiatry and Neurobiology, and in the Child Study Center; Director, Yale Program for Research on Impulsivity and Impulse Control Disorders and Director, Women and Addictive Disorders, Yale University School of Medicine

Stefania Prendes-Alvarez, M.D: Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine

Scott L. Rauch, M.D.: Professor of Psychiatry, Harvard Medical School; President, Psychiatrist in Chief, and Rose-Marie and Eijk van Otterloo Chair of Psychiatry, McLean Hospital; Chair of Partners Psychiatry and Mental Health

Charles F. Reynolds, III, M.D.: Professor, Departments of Psychiatry and of Behavioral and Community Health Sciences, and Director of the Aging Institute and the Center of Excellence in the Prevention and Treatment of Late Life Mood Disorders, University of Pittsburgh Schools of the Health Sciences

Peter P. Roy-Byrne, M.D.: Professor, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine

Moira A. Rynn, M.D.: Division Director, Child & Adolescent Psychiatry; Professor of Clinical Psychiatry, Department of Psychiatry, New York State Psychiatric Institute/Columbia University

Alan F. Schatzberg, M.D.: Professor of Psychiatry and Behavioral Science and Director, Mood Disorders Center, Stanford University School of Medicine

Robert A. Schnoll, Ph.D.: Associate Professor of Psychiatry, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania

R. Taylor Segraves, M.D., Ph.D.: Chair, Department of Psychiatry, Metrohealth Medical Center, Cleveland

Larry J. Siever, M.D.: Professor, Department of Psychiatry, Icahn School of Medicine at Mount Sinai

David L. Sultzer, M.D.: Professor and Director, Geriatric Psychiatry Department, VA Greater Los Angeles Healthcare System, and Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA

R. Dale Walker, M.D.: Professor and Director, One Sky Center, Departments of Psychiatry, Public Health and Preventive Medicine, Oregon Health & Science University

Paula L. Wilbourne, Ph.D.: Director, Addiction Treatment Services, VA Palo Alto Health Care System (152MPD)

Rachel Yehuda, Ph.D.: Professor of Psychiatry and Neuroscience, Director of the Traumatic Stress Studies Division, Icahn School of Medicine at Mount Sinai; Mental Health Patient Care Center Director, James J. Peters VAMC

Summary of Treatments That Work

Syndrome	*Treatments*	*Standards of Proof*	*References*
Agoraphobia (moderate to severe)	**Psychosocial Treatments** • The clinical efficacy of *situational in vivo exposure* for patients with moderate to severe agoraphobia has been established.	• A substantial number of excellent studies, largely type 1	Chapter 14, pp. 409–462 (Barlow, Conklin, & Bentley)
Anorexia Nervosa	**Psychosocial Treatments** • Anorexia nervosa remains extremely challenging to treat. • Initial studies suggest that *cognitive-behavioral therapy (CBT)* may be associated with improved outcome in both the acute and maintenance phases of treatment. • Adapting *CBT* and *Specialist Supportive Clinical Management* for severe and enduring anorexia nervosa can result in better engagement in treatment and significant clinical improvement. **Psychopharmacological Treatments** • The impact of atypical antipsychotic medication, most often *olanzapine*, on weight gain and eating disorder psychopathology in anorexia nervosa has recently been assessed. Results have generally been mixed, inconsistent, and small. • The effectiveness of *fluoxetine* following weight restoration in anorexia nervosa has also been studied; it did not have an impact on time to relapse, weight gain or loss, or core eating disorder pathology above and beyond CBT, and there was no evidence it was superior to placebo.	• A number of randomized controlled trials (RCTs): More methodologically rigorous studies are needed	Chapter 20, pp. 641–658 (Pike, Gianini, Loeb, & Le Grange)

Syndrome	*Treatments*	*Standards of Proof*	*References*
Attention-Deficit/ Hyperactivity Disorder (ADHD)	**Combined Treatments** • Combined behavioral and medication treatments appear to reduce the needed dose or intensity of each intervention.	• A significant number of well-designed studies, primarily type 1	Chapter 3, pp. 55–84 (Pfiffner & Maack)
	Psychopharmacological Treatments • *Psychostimulants* are highly effective in reducing core symptoms of ADHD in children and adults.	• A very large number of RCTs, primarily type 1	Chapter 4, pp. 85-140 (Kass, Posner, & Greenhill)
	Psychosocial Treatments • Of the nonpharmacological treatment approaches for ADHD in children, behavioral interventions have the largest evidence base. • These interventions include *behavioral parent training (BPT)*, *behavioral classroom management (BCM)*, *child skills training (CST)*, *behavioral multicomponent interventions (BMI)*, and *multimodal treatment (MT)*, which combines behavioral interventions and medication.	• A substantial number of RCTs for most of these behavioral treatments, primarily type 1	Chapter 3, pp. 55–84 (Pfiffner & Maack)
Binge Eating Disorder	**Psychosocial Treatments** • *CBT* and *interpersonal therapy (IPT)* have been shown to be the most efficacious in reducing symptoms and improving psychological outcomes. However, these treatments have generally been unsuccessful in producing significant, maintainable weight loss.	• A number of RCTs (type 1 and type 2)	Chapter 20, pp. 641–658 (Pike, Gianini, Loeb, & Le Grange)
	Psychopharmacological Treatments • Three drugs are currently approved by the U.S. Food & Drug Administration (FDA) for treating obesity: *orlistat*, *lorcaserin*, and *phentermine-topiramate*. Of these, only orlistat (a lipase inhibitor) has been studied as a treatment for obese individuals with binge eating disorder, although topiramate (without phentermine) has also been examined. Weight loss associated with these drugs has generally not been maintained.	• A number of type 1 and type 2 RCTs	Chapter 20, pp. 641–658 (Pike, Gianini, Loeb, & Le Grange)

Syndrome	*Treatments*	*Standards of Proof*	*References*
	• In these studies, either tricyclic antidepressants (*imipramine*) or selective serotonin reuptake inhibitors (SSRIs; *fluoxetine*, *fluvoxamine*, *sertraline*, *citalopram*) were used for short-term treatment either in conjunction with psychotherapy or alone. Overall, binge remission rates were significantly higher at the end of treatment in the active medication treatments compared with placebo (40.50% vs. 22.22%). However, these periods of treatment were relatively short and the study with the longest duration did not find a significant difference between fluoxetine and placebo groups.	• A 2008 meta-analysis of seven studies	
Bipolar Disorder in Adults	**Psychopharmacological Treatments**		
	• The pharmacological management of bipolar disorder involves the treatment of acute manic, hypomanic, mixed, and depressive episodes, as well as the prevention of further episodes.		Chapter 8, pp. 237–272 (Keck & McElroy)
	• *Lithium*, *divalproex*, *carbamazepine*, *haloperidol*, *risperidone*, *olanzapine*, *quetiapine*, *ziprasidone*, *aripiprazole*, and *asenapine* have demonstrated efficacy in the treatment of acute mania.	• Many type 1 & type 2 RCTs	
	• Although pharmacological treatment of acute bipolar depression remains understudied, *lithium*, *olanzapine*, *olanzapine-fluoxetine*, *quetiapine*, *lurasidone*, *tricyclic antidepressants*, *monoamine oxidase inhibitors (MAOIs)*, and *fluoxetine* have shown efficacy. • *Lithium*, *lamotrigine*, *olanzapine*, *aripiprazole*, *quetiapine*, and *resperidone* have shown efficacy in relapse prevention.	• A large number of RCTs	

Syndrome	*Treatments*	*Standards of Proof*	*References*
	Combined Treatments		
	• Although pharmacological interventions remain the primary treatment for bipolar disorder, adjunctive psychosocial interventions can increase adherence to medication regimens, decrease hospitalizations and relapses, decrease severity of symptoms, improve quality of life, and enhance mechanisms for coping with stress.	• Four type 1 & 2 studies	Chapter 10, pp. 307–326 (Muralidharan, Miklowitz, & Craighead)
	• *Group psychoeducation* leads to lower rates of recurrence and greater adherence to medication among remitted bipolar patients at both short- and long-term follow-up.	• Three type 1 studies	
	• *Family-based intervention* has been effectively combined with pharmacotherapy to reduce recurrences and hospitalization rates in adult patients.	• Three type 1 studies	
	• *Family psychoeducation and skills training* may be effective adjuncts to pharmacotherapy for bipolar spectrum children and adolescents and youths at high risk for bipolar disorder.		
Bipolar Disorder in Children and Adolescents	**Pharmacological Treatments**		
	• Practice guidelines recommend pharmacotherapy with mood stabilizers or second generation antipsychotics as the first-line treatment for pediatric bipolar disorder. Currently, *lithium*, *risperidone*, *aripiprazole*, *quetiapine*, and *olanzapine* are approved by the FDA for treating bipolar disorder in children and adolescents.	• A number of type 1 and type 2 RCTs	Chapter 9 , pp. 273–306 (Goldberg, Martin, Biernacki, & Rynn)
	Psychosocial Treatments		
	• A growing body of literature also suggests the efficacy of psychosocial interventions with *family psychoeducation* and *skills building* as adjunct treatments to pharmacotherapy.		

Syndrome	*Treatments*	*Standards of Proof*	*References*
Borderline Personality Disorder	**Psychosocial Treatments:**		
	• A meta-analysis found statistically significant effects indicating a beneficial effect of *dialectical behavior therapy (DBT)* over treatment as usual for improvements in anger (two RCTs), parasuicidality (three RCTs), and mental health (two RCTs). All of these effects were moderate to large in size.	• A substantial meta-analysis and a number of RCTs	Chapter 27, pp. 851–870 (Crits-Christoph & Barber)
	• Versions of *psychodynamic therapy* have also shown positive outcomes comparable to DBT.	• Two type 1 RCTs	
	Psychopharmacological Treatments		
	• In borderline personality disorder, evidence of moderate effectiveness is strongest for second-generation antipsychotics and mood stabilizers. However, medications have limited effectiveness and are still viewed as adjunctive to other forms of treatment, particularly psychotherapy.	• A number of RCTs	Chapter 28, pp. 871–906 (Perez-Rodriguez & Siever)
Bulimia Nervosa	**Psychosocial Treatments**		
	• There is strong cumulative support for *CBT* as the treatment of choice for bulimia nervosa. • The utility of *IPT* and *pharmacotherapy* as appropriate alternative treatments in the treatment of bulimia nervosa has also been suggested.	• Many well-designed type 1 and type 2 studies	Chapter 20, pp. 641–658 (Pike, Gianini, Loeb, & Le Grange)
	Psychopharmacological Treatments		
	• *Fluoxetine* is FDA approved for the treatment of bulimia nervosa.	• A substantial number of RCTs	
Conduct Disorder and Oppositional Defiant Disorder	**Psychosocial Treatments**		
	• Several psychosocial interventions have shown strong evidence of efficacy with children and adolescents with conduct disorder. They include *parent management training*, *multisystemic therapy*, *multidimensional treatment foster care model*, *cognitively based treatments*, *functional family therapy*, *brief strategic family therapy*, and *the Good Behavior game*.	• A number of well-designed RCTs, largely type 1, for each intervention	Chapter 5, pp. 141–174 (Kazdin)

Syndrome	*Treatments*	*Standards of Proof*	*References*
	Psychopharmacological Treatments		
	• Psychopharmacological management with FDA-approved agents (*stimulants*, *second-generation antipsychotics*, and *mood stabilizers*) decreases the defiant and aggressive behavior characteristic of disruptive behavior disorders, including conduct disorder and oppositional defiant disorder.	• A number of RCTs, type 1 and type 2	Chapter 4, pp. 85–140 (Kass, Posner, & Greenhill)
Depressive Disorder in Children and Adolescents	**Pharmacological Treatments**		
	• In moderate to severe cases of pediatric depression, medication treatment is recommended, with or without CBT. Currently, *fluoxetine* and *escitalopram* are the only antidepressants approved by the FDA for acute pediatric depression.	• A substantial number of type 1 and type 2 RCTS	Chapter 12 , pp. 355–380 (Biernacki, Martin, Goldberg, & Rynn)
	Psychosocial Treatments		
	• Practice guidelines recommend psychosocial interventions for mild or brief cases of pediatric depression.	• A number of RCTs	
	• Among psychosocial interventions, *CBT* and *IPT for adolescents* (IPT-A) have the largest evidence base for treatment of depressed youth.		
	Combination Treatments		
	• Combination treatment with *CBT* and *antidepressant medication* is superior to treatment with either modality alone.	• A number of RCTs	
Erectile Dysfunction	**Psychopharmacological Treatments**		
	• Investigations have demonstrated the efficacy of *phosphodiesterase type 5 inhibitors* for the treatment of erectile problems of mixed etiologies.	• Well-controlled double-blind multisite (type 1) interventions	Chapter 22, pp. 699–730 (Segraves)
Gambling Disorder	**Psychosocial Treatments**		
	• Specific behavioral (e.g., *CBT*) treatments significantly reduce the symptoms of gambling disorder in the short term compared to waitlist or placebo.	• Several controlled outcome studies (type 1 & type 2)	Chapter 25, pp. 801–826 (Grant, Odlaug, & Potenza)
	• Limited long-term effects of manual-based CBT have also been observed.	• Several small studies	

Syndrome	*Treatments*	*Standards of Proof*	*References*
	Psychopharmacological Treatments • Specific pharmacological (e.g., *naltrexone*, *nalmefene*, *lithium*) treatments significantly reduce the symptoms of gambling disorder in the short term compared to waitlist or placebo. • The long-term benefits of psychopharmacological treatment have not been adequately tested.	• Several controlled outcome studies (type 1 & type 2)	Chapter 25, pp. 801–826 (Grant, Odlaug, & Potenza)
	Combined Treatments • The potential benefit of combining behavioral and drug treatments for gambling disorder remains understudied.		
Generalized Anxiety Disorder	**Psychopharmacological Treatments** • The pharmacological treatments of choice for generalized anxiety disorder are *buspirone* and *antidepressants*, including *SSRIs* and *venlafaxine*.	• A large number of type 1 and type 2 RCTs	Chapter 15, pp. 436–506 (Kimmel, Roy-Byrne, & Cowley)
	Psychosocial Treatments • Recent studies suggest that *CBT* approaches are most successful for generalized anxiety disorder. Specifically, newer variants of CBT that target intolerance of uncertainty or metacognitive beliefs about worry show promising levels of efficacy and superiority to alternative treatments.	• A number of recent well-designed RCTS	Chapter 14, pp. 409–462 (Barlow, Conklin, & Bentley)
Hypersomnolence Disorder and Narcolepsy	**Combined Treatments** • The mainstay of treatment is *pharmacological*, although *adjunctive behavioral therapy* plays a role in adapting to the situation.		Chapter 21, pp. 659–698 (Burman, Buysse, & Reynolds)
	Psychopharmacological Treatments • Treatment is similar for both hypersomnolence and narcolepsy. Treatment aims at symptom control to allow patients to live full personal and professional lives.		Chapter 21, pp. 659–698 (Burman, Buysse, & Reynolds)
	• Medications include *stimulants* (including *amphetamines* and related drugs) and *modafinil* and *armodafinil*. • First-line treatment for cataplexy consists of *antidepressants* (*venlafazine*, *desmethylvenlafaxine*, *duloxetine*, *fluoxetine*).	• A substantial number of well-designed RCTs	

Syndrome	*Treatments*	*Standards of Proof*	*References*
Insomnia	**Psychosocial Treatments** • *Multicomponent CBT for insomnia (CBT-I), stimulus control therapy, and sleep restriction therapy* appear to be most efficacious in reducing sleep latency and improving sleep consolidation by changing behaviors, habits, and cognitions that interfere with sleep. • Behavioral approaches are comparable to medications in efficacy and have been found to be more durable.	• A number of type 1 and type 2 studies	Chapter 21, pp. 659–698 (Burman, Buysse, & Reynolds)
	Psychopharmacological Treatments • The *benzodiazepine receptor agonists* have the best-established scientific basis for use in insomnia. • The melatonin agonist *ramelteon (Rozerem)* is also FDA approved for the treatment of insomnia.	• Many RCTs, both type 1 and type 2	Chapter 21, pp. 659–698 (Burman, Buysse, & Reynolds)
Combination Treatment for Major Depressive and Anxiety Disorders	• There is little evidence that combined psychosocial and medication therapy is superior to either alone in the treatment of mood and anxiety disorders. • Exceptions are adolescents with major depression and those with five or more recurrent moderate to severe episodes as well as augmentation of CBT or IPT in partial responders and nonresponders.		Chapter 16, pp. 507–544 (Aaronson, Katzman, & Moster)
Major Neurocognitive Disorders	**Psychopharmacological Treatments** • The treatment of major neurocognitive disorders, including Alzheimer's disease, is currently symptomatic; the goal is to temporarily improve symptoms or slow the progression of cognitive, psychiatric, and behavioral symptoms.		Chapter 26, pp. 827–850 (Nie & Sultzer)
	• While *cholinesterase inhibitors* and *memantine* are standard treatments for Alzheimer's disease at this time, the literature demonstrates only modest benefit, and critics cite the variability in methodological quality of the trials.	• A very large number of type 1 and type 2 studies	

Syndrome	*Treatments*	*Standards of Proof*	*References*
Obsessive-Compulsive Disorder (OCD)	**Combined Treatments** • There is overwhelming evidence of the most rigorous type supporting the efficacy *of serotonin reuptake inhibitors (SRIs)* in the treatment of OCD. • Along with SRIs, *behavior therapy* must be considered a viable first-line therapy. • The best available data suggest that *behavior therapy*, and perhaps *cognitive therapy*, are at least as effective as medication in some instances and may be superior with respect to risks, costs, and enduring benefits.	• Many type 1 RCTs	Chapter 17, pp. 545–570 (Dougherty, Rauch, & Jenike)
Panic Disorder (with or without Agoraphobia)	**Psychosocial Treatments** • The efficacy of *CBT* for persons with panic disorder with or without agoraphobia has been established. These treatments include some combination of *cognitive elements*, *exposure to interoceptive sensations similar to physiological panic sensations*, *in vivo exposure*, and *breathing retraining*.	• A substantial number of type 1 studies	Chapter 14, pp. 409–462 (Barlow, Conklin, & Bentley)
	• Successful dissemination of *CBT* for panic disorder has recently been established in effectiveness trials.	• Several large effectiveness trials (type 1)	
	Psychopharmacological Treatments • *SSRIs* are now considered the first-line pharmacological treatment for panic disorder, based on their low rate of side effects, lack of dietary restrictions, and absence of tolerance.	• A large number of type 1 and type 2 clinical trials	Chapter 15, pp. 436–506 (Kimmel, Roy-Byrne, & Cowley)
Posttraumatic Stress Disorder (PTSD)	**Psychosocial Treatments** • PTSD treatments work better than treatment as usual; average effect sizes are in the moderate to high range. • A variety of treatments have been established as effective, with no one treatment having superiority. Both present-focused and past-focused models work (neither consistently outperforms the other). • Consistent, significant differences between active treatments have not been reported.	• RCTs with treatment as usual, minimal attention, and waitlist controls	Chapter 18, pp. 571–592 (Najavits & Anderson)

Syndrome	*Treatments*	*Standards of Proof*	*References*
	Psychopharmacological Treatments • Although psychotherapy is considered the first line of treatment for PTSD, advances have been made in the pharmacological treatment of this disorder as well. • Antidepressants are still the first-line pharmacological treatment for PTSD. The SSRIs (e.g., *fluoxetine*, *sertraline*, and *paroxetine*) are efficacious in reducing PTSD-specific symptoms and improving global outcome. Other individual agents found to be efficacious include the tricyclic antidepressant *imipramine* and the MAOI *phenelzine*.	• A large number of RCTs, both type 1 and type 2	Chapter 19, pp. 593–640 (Golier, Michaelides, Genovesi, Chapman, & Yehuda)
Premature Ejaculation	**Psychopharmacological Treatments** • *Serotonergic antidepressants* delay ejaculation in men with premature ejaculation.	• A number of well-designed RCTs (type 1)	Chapter 22, pp. 699–730 (Segraves)
	Psychosocial Treatments • There is suggestive evidence for the efficacy of CBT in the treatment of sexual dysfunction in both sexes, although the number and methodological rigor of such studies are limited and the effect sizes tend to be smaller than those of studies of pharmacological therapies.	• A limited number of type 1 and type 2 RCTs	Chapter 22, pp. 699–730 (Segraves)
Schizophrenia Spectrum Disorders	**Psychopharmacological Treatments** • The first antipsychotic drug, *chlorpromazine*, was introduced in 1954, followed by several similar drugs. With the later introduction *of clozapine*, *risperidone*, *olanzapine*, *quetiapine*, *ziprasidone*, *aripiprazole*, and more recently *paliperidone*, *iloperidone*, *asenapine*, and *lurasidone*, antipsychotic drugs are often classified as first generation or typical (chlorpromazine-like) versus second generation or atypical (clozapine-like). • Both of these broad classes of medications have been demonstrated to safely improve psychotic symptoms in the acute phase of the illness and to reduce the risk of relapse in the maintenance phase of treatment.	• Many type 1 and type 2 controlled studies	Chapter 6, pp. 175–216. (Abbas & Lieberman)

Syndrome	*Treatments*	*Standards of Proof*	*References*
	• Because of the limited efficacy of antipsychotic medication in resolving the full range of schizophrenic psychopathology, adjunctive treatments are often used to reduce morbidity. Drugs such as *benzodiazepines*, *lithium*, *carbamazepine*, *valproic acid*, *antidepressants*, *glutamate agonists*, and *dopamine agonists* have been used alone and in combination with antipsychotic drugs to improve treatment response.	• Many type 1 and type 2 controlled studies	
	Psychosocial Treatments		
	• Cognitive remediation (CR) and social cognitive training (SCT) have been increasingly studied as behavioral interventions to improve disorder-linked cognitive and social cognitive deficits in schizophrenia. They appear to hold considerable promise for improving disorder outcome.	• Over 80 controlled studies and seven meta-analyses of CR and 20 controlled studies and one meta-analysis on SCT have been conducted to date.	Chapter 7, pp. 217–236 (Kurtz)
Sexual Dysfunction in Women after Oophorectomy	**Psychopharmacological Treatments**		
	• *Transdermal testosterone* restores sexual function in women after oophorectomy.	• A number of well-designed RCTs (type 1)	Chapter 22, pp. 699–730 (Segraves)
Social Anxiety Disorder	**Psychopharmacological Treatments**		
	• *SSRIs* and *venlafaxine* are attractive first-line treatments for social anxiety disorder.	• A substantial number of type 1 RCTs	Chapter 15, pp. 463–506 (Kimmel, Roy-Byrne, & Cowley)
	Psychosocial Treatments		
	• The most common treatment approaches for social anxiety disorder include *social skills training*, *relaxation techniques*, *exposure-based methods*, and *multicomponent cognitive-behavioral treatments*; the latter, along with exposure-based procedures, attain the highest level of treatment efficacy.	• Many type 1 RCTs	Chapter 14, pp. 409–462 (Barlow, Conklin, & Bentley)
Specific Phobias	**Psychosocial Treatments**		
	• The treatment of choice for specific phobias is *exposure-based procedures*, particularly *in vivo exposure*.	• A large number of type 1 studies	Chapter 14, pp. 409–462 (Barlow, Conklin, & Bentley)

Syndrome	*Treatments*	*Standards of Proof*	*References*
Substance Use Disorders	**Combined Treatments**		
	• The treatment of substance use disorders with medications is well established, although most experts agree that to be successful pharmacological interventions must be combined with psychosocial therapies.	• A number of well-designed RCTs	Chapter 24, pp. 763–800 (McKay, Kranzler, Kampman, Ashare, & Schnoll)
	Psychopharmacological Treatments		
	• The treatment of alcohol use disorder can now be enhanced by three approved medications based on different mechanisms of action: *disulfiram*, *naltrexone*, and *acamprosate*. A long-acting version of naltrexone is approved by the FDA.	• A large number of type 1 and type 2 RCTs for each substance	Chapter 24, pp. 763–800 (McKay, Kranzler, Kampman, Ashare, & Schnoll)
	• The use of nicotine replacement therapy to induce and maintain smoking cessation significantly increases abstinence rates, as have non-nicotine treatments such as *bupropion* and *varenicline*.	• A large number of type 1 and type 2 controlled trials	
	• *Methadone maintenance* treatment has consistently shown efficacy in the treatment of opioid use disorders; the partial opioid agonist *buprenorphine* has substantially expanded the options for treating this disorder.	• A substantial number of type 1 controlled trials	
	Psychosocial Treatments		
	• The most effective psychosocial treatments for substance use disorders include *cognitive-behavioral interventions*, *motivational interviewing and motivational enhancement*, *contingency management*, *community reinforcement*, *behavioral couples and family therapies*, and *12-step facilitation approaches*.	• A substantial number of type 1 and type 2 trials for each mode of intervention	Chapter 23, pp. 731–762 (Blonigen, Finney, Wilbourne, & Moos)
	• *Brief interventions* are quite effective in the treatment of substance use disorders, especially in those with mild and moderate disorders.	• A very large number of clinical trials	
Trichotillomania	**Psychosocial Treatments**		
	• *CBT* is effective for trichotillomania.	• "Several studies"	Chapter 25, pp. 801–826 (Grant, Odlaug, & Potenza)
	Psychopharmacological Treatments		
	• Two studies (both type 1) in adults (N-*acetylcysteine*, *olanzapine*) for this disorder have shown promise.	• Two type 1 studies	

Syndrome	*Treatments*	*Standards of Proof*	*References*
Unipolar Depression (Major Depressive Disorder [MDD])	**Combined Treatments** • The data for outcomes of psychosocial and pharmacological interventions for major depressive episodes suggest that the two treatment modes are equally efficacious. Meta-analyses lend support for the superior effectiveness of combined psychosocial and pharmacological treatments with chronic depression.	• Many well-designed RCTs	Chapter 13, pp. 381–408 (Craighead, Johnson, Carey, & Dunlop)
	Psychopharmacological Treatments • The treatment of unipolar depression with *antidepressant medication* is well established. • *Tricyclic antidepressants*, the first to be studied extensively, were consistently and significantly more efficacious than placebo. • Tricyclics have now been replaced as the first-line treatment of depression by *SSRIs (fluoxetine, sertraline, paroxetine, citalopram, escitalopram)*, as well as by *serotonin norepinephrine reuptake inhibitors (SNRIs: venlafaxine, duloxetine, desvenlafaxine, levomilnacipran)*. • Other compounds, including *bupropion, vortioxetine, vilazodone*, and *mirtazapine*, have also proven efficacious. • *MAOIs* have generally been reserved for treatment-refractory patients. • Combination and augmentation therapy practices are gaining in popularity for patients who are partial responders and nonresponders to monotherapy.	• Scores of RCTs involving hundreds of thousands of patients	Chapter 11, pp. 327–354 (Prendes-Alvarez, Schatzberg & Nemeroff)
	Psychosocial Treatments • Behavior therapy (BT), CBT, and IPT have each been shown to be effective psychosocial interventions for patients meeting criteria for major depressive disorder.	• Each has been shown to be efficacious by at least two type 1 or type 2 RCTs, as well as numerous meta-analytic reports of the literature.	Chapter 13, pp. 381–408 (Craighead, Johnson, Carey, & Dunlop)

A GUIDE TO TREATMENTS THAT WORK

1

Challenges to Implementing Evidence-Based Treatments

Jack M. Gorman
Peter E. Nathan

The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; *DSM-5*; American Psychiatric Association, 2013) was published in May 2013, six months before this chapter was written, and has been the target of intense criticism through most of the years of its development. This chapter undertakes a detailed examination of two of the most significant issues raised by critics of *DSM-5*. Neither is new, and both are highly relevant to a number of issues addressed in this book. The first matter recognizes the continued absence of viable biomarkers of specific diagnoses. Despite intense efforts by neuroscientists to identify such markers, and strong interest in them by the authors of successive editions of the *DSM*, including *DSM-5*, biomarkers are not a feature of the 2013 nomenclature. We will argue that the problem rests at least as much with the *DSM* system as it does with progress made by neuroscientists. The second question concerns what many critics view as the inordinate influence of the pharmaceutical industry—Big Pharma—on the highly troubling problem of overdiagnosis that began with *DSM-III* (American Psychiatric Association, 1980). These two issues, clearly related to each other and both likely to grow markedly in importance over time, deserve recognition and discussion here.

DSM-5 AND ITS DETRACTORS

Three books critical of *DSM-5* (Burns, 2013; Frances, 2013; Greenberg, 2013) appeared coincident with its publication in May 2013. Many articles, op-ed pieces, and letters to the editor, written by an array of prominent figures in psychiatry and the other mental health professions, also appeared in recent years in prominent print media, including the *New York Times*, *Washington Post*, and *Psychiatric Times*; most were highly critical of both the *DSM-5* process and its emerging content. Numerous critical talks were delivered at public and professional meetings, and a seemingly endless array of concerns about the direction and content of *DSM-5* have been expressed in diverse social media.

Has the volume of criticism of *DSM-5* been greater than that leveled at its predecessors? Almost certainly so, in part because the scope and reach of commentaries facilitated by social media are so much greater than was possible before, and in part because the attack on *DSM-5*, which began very early, before the Work Groups and Task Force were fully constituted, was led by Allen Frances, a highly credible critic because of his lead role in the development of *DSM-IV* (American Psychiatric Association, 1994) and his status as a prominent psychiatric scientist and administrator.

Most criticisms of *DSM-5* are not new; they were also voiced in reaction to earlier versions of the nomenclature. To this end, even though the first two editions of the nomenclature—*DSM-I* (American

Psychiatric Association, 1952) and *DSM-II* (American Psychiatric Association, 1968)—were lauded as the nation's first national psychiatric taxonomies, they were criticized because many of their diagnostic formulations seemed unduly influenced by psychoanalytic theory; because of the almost total absence of empirical data in support of the diagnostic syndromes; and because most of those syndromes were described so briefly and sketchily that they typically generated diagnoses on which clinicians could not agree.

Substantial changes in the diagnostic system introduced in *DSM-III* (1980) and largely maintained in *DSM-IV* (1994) and *DSM-5* (2013) markedly increased diagnostic reliability. A number of diagnoses in the latter nomenclatures were based on empirical data from specifically commissioned field trials. Nonetheless, these instruments too were strongly criticized—for effecting an almost threefold increase in the number of diagnoses, especially for children and adolescents; for introducing a number of new diagnoses largely unsupported by empirical research; and for attempting to "medicalize" diagnosis by highlighting the efficacy of psychopharmacological treatments and the promise of emerging neuroscience findings that many critics felt were unwarranted (Langenbucher & Nathan, 2006; Oltmanns & Castonguay, 2013; Widiger & Edmundson, 2011).

The duration and intensity of attacks on *DSM-5* represent one major difference between the reception accorded that instrument and its predecessors. The other differences stem from the force of criticisms largely directed toward the two matters on which this chapter focuses. Both matters were briefly raised by critics of *DSM-III*, elaborated on by critics of *DSM-IV*, and elevated further to crescendos of concern in *DSM-5*. Both issues seem likely to continue to affect diagnosis and treatment, as well as the future of the *DSM*.

THE PROMISE OF BIOMARKERS, AS YET UNFULFILLED

In the years before the third edition of *DSM* appeared in 1980, hope was expressed that efforts to correlate early findings on brain structure and function with psychiatric disorders would yield linkages with selected *DSM* categories of mental illness. Despite these hopes, expressed by leaders of American psychiatry and psychology as well as many of those involved in *DSM-III* and *DSM-IV* development efforts, breakthroughs sufficient to justify their inclusion in these nomenclatures did not occur. Nonetheless, especially given impressive gains in analytic methods and technical procedures and exciting new findings in neuroscience, it was anticipated that increasingly sophisticated and productive studies of neural transmission, molecular neuroscience, systems neuroscience, genetics, and epidemiology, in accelerating trajectory, would finally anchor selected mental disorder diagnoses to firm neuroscience bases. The leaders of the *DSM-5* development process were outspoken in their anticipation of nothing less at the commencement of the *DSM-5* development process. One of the most important reasons for the intensity of the quest was the belief that such work would finally enable development of rationally designed and, hence, more effective treatments.

Despite these expectations, however, biomarkers and data from neuroscience research are not a prominent feature of *DSM-5*. Allen Frances, one of the most persistent of those recognizing the failure of continuing efforts to relate findings from contemporary neuroscience and neurobiological research to specific DSM-5 diagnoses, presents it this way: "The excessive DSM-5 ambition to effect a paradigm shift in psychiatric diagnosis [included] the unrealistic goal of transforming psychiatric diagnosis by somehow basing it on the exciting findings of neuroscience. This would be wonderful were it possible, but the effort failed for the obvious reason that it is still a bridge too far" (2013, p. 171). Other prominent psychiatrists, including Thomas Insel, director of the National Institute of Mental Health (NIMH); Steven Hyman, a former NIMH director; and Eric Kandel, a psychiatric neuroscientist and Nobel laureate, have also questioned continued reliance on behavioral diagnosis in favor of diagnosis based on neurobiologic markers and have expressed great disappointment at the inability of researchers to date to replace the behavioral diagnosis paradigm that continues to characterize the DSM with a neuroscience-based diagnostic system that would be more rational and more closely tied to treatment options. Opinion is mixed, however, on the issue: Is there already enough neurobiologic evidence to reconfigure components of the diagnostic nomenclature, or is such an effort entirely premature and must it await substantial further developments?

Although progress to date in developing reliable, neuroscience-based correlates of specific psychiatric

disorders has not met the goal of validating specific *DSM-5* categories of illness, a closer look at the research, in our view, yields substantial promise. Indeed, to appreciate how much progress has been made it is often necessary to set aside *DSM* categories, which often mask what has been accomplished in the laboratory.

As briefly noted above, critics of *DSM-III* (American Psychiatric Association, 1987), *DSM-IV*, *DSM-IV-TR* (American Psychiatric Association, 2000), and *DSM-5* argued that all of these nomenclatures constituted covert attempts to "medicalize" psychiatry by their emphases on inherited aspects of mental disorders and pharmacological therapies. In fact, neuroscience has been just as likely to validate experiential causes and psychosocial treatments for psychiatric disorders. Whereas *DSM-I* and *DSM-II* were disparaged because of their reliance on psychoanalytic terms and theory, the latter-day *DSM*s were thought to want to eliminate theory of all kinds in order to reflect the "new psychiatry" of neurotransmitters, the familial recurrence of psychiatric illness, and psychopharmacology. Many of the critics of *DSM-5*, however, insist that there is in fact no proven neuroscientific basis to most if not all psychiatric disorders and that the effort to relate the "bench to the bedside" is based on wishful thinking. The attempt to give psychiatric diagnosis a physical/medical basis is seen as benefitting the pharmaceutical industry and psychiatry to the detriment of psychotherapy and the nonmedical mental health professions. Indeed, as we noted previously and detail below, the other major concern raised by critics of *DSM-5* is that "Big Pharma" has exerted undue influence on our understanding of which psychopharmacological treatments are efficacious.

Regardless of whether one supported or opposed the introduction of *DSM-5*, it is widely believed that to date neuroscience has offered few insights that would establish the validity of individual *DSM* categories. For example, there is not yet a discrete biology for such common conditions as 296.3 (major depressive episode), 295.90 (schizophrenia), or 309.81 (posttraumatic stress disorder). Most of the changes from *DSM-IV* to *DSM-5* are based on epidemiological evidence. Hence, critics have sounded a discouraging alarm that decades of extensive neuroscientific research have been largely fruitless in developing a biological basis for the categorization of mental disorders. Soul searching for some has turned to despair.

Indeed, most of the initial attempts to explain mental disorders on the basis of biomarkers *have* turned out to be inadequate. In the years following the introduction of medications to treat psychiatric disorders, psychopathology was attributed to abnormalities in the neurotransmitter systems targeted by each kind of medication. Thus, because the antipsychotic drugs blocked dopamine effects in the brain, schizophrenia was ascribed to an excess of central nervous system dopamine. The new tricyclic and monoamine oxidase inhibitor antidepressant drugs increased the concentrations of the neurotransmitters serotonin and norepinephrine, and so depression was labeled a serotonin/norepinephrine deficiency disease. These ideas held remarkable traction for more than 20 years, but by 1980 they were already proving to be deficient in explaining what really is wrong in the brains of people with schizophrenia or depression. No one was able to show that there actually is too much dopamine in the brains of people with schizophrenia or too little serotonin in the brains of people with depression. Similarly, the discovery that psychiatric illnesses run in families, based on family, twin, and adoption studies, created the assumption that ultimately all mental disorders would turn out to be caused by genetic mutations. Because such mutations have proven just as elusive for mental disorders as they have for most other chronic illnesses (e.g., diabetes, congestive heart failure, obesity, and kidney failure), it has increasingly seemed to many that the search for a genetic basis for mental illness might also be futile.

Yet this pessimism may be misplaced, for there are indeed strong signs that some definite conclusions about the biology of mental disorders can be made on the basis of preclinical and clinical research. The problem for the current diagnostic system is that these conclusions do not map well onto specific *DSM-5* categories. Thomas Insel, NIMH director, has stressed this point in the creation of the Research Domain Criteria (RDoC) (Cuthbert & Insel, 2013). Rather, a review of progress in the neuroscience of mental disorders suggests that biological findings adhere to specific types of psychopathology that cut across these categories. In other words, the disappointingly low validity of *DSM-5* categories of illness may reflect the fact that biological findings appear to account for symptoms of illness that cut across those categories. Although a great deal of this work involves animal models of psychopathology, much of it is substantiated by clinical findings using the

increasingly sophisticated tools of neuroimaging. In a few instances, this work has led to insights into the development of new therapeutic interventions. It is extremely important to bear in mind, however, that neuroscience and psychopharmacology are not coextensive disciplines. Modern neuroscience, much of which is conducted by nonpsychiatrists, has been as likely to link psychopathology to adverse life experiences and stress as to genetic mutations, and the treatments it validates include a variety of psychosocial interventions, not just drugs.

In this section of the chapter, we will briefly consider data from four examples of this development, recognizing that the list is hardly exhaustive and that even with these four there are still ample reasons for caution before making final pronouncements about the biological foundation of psychopathology. This kind of thinking may be synchronous with what will occur in developing the NIMH RDoC. We also review here solid neuroscientific evidence for a pathway—adverse early childhood experience—that increases the risk for almost all forms of psychopathology and therefore should inform the development of new interventions. In brief, this review encompasses the following:

1. Anxiety disorders and depression share disruption in the normal restraint of the medial prefrontal cortex (mPFC) over the activity of the amygdala, leading to a fearful state and inability to make rational assessments of threat. Interventions that restore the normal balance between mPFC and amygdala are therapeutic for fear-based disorders.
2. Obsessive and compulsive behaviors involve disruption of the sensitivity of pathways from the orbitofrontal cortex (OFC) to the ventral striatum. This applies to such behaviors included as parts of the diagnostic criteria for a wide variety of disorders, including obsessive-compulsive disorder, autism, and addiction.
3. Psychosis, regardless of whether it occurs in an individual with schizophrenia, bipolar disorder, major depression, or amphetamine abuse, is linked to excess dopamine neurotransmission and stimulation of the dopamine type 2 (D_2) receptor in the ventral striatum. Medications that reduce positive psychotic symptoms (hallucinations, delusions, and thought disorder) all inhibit dopamine binding to the D_2 receptor.
4. Addiction to most substances, including alcohol, cocaine, heroin, nicotine, and amphetamines, is accompanied by desensitization of the dopaminergic pathway from the ventral tegmental area (VTA) in the brain stem to the nucleus accumbens (NA) in the limbic cortex.
5. Adverse early life experience disrupts multiple aspects of brain biology, including the epigenetic control of gene expression, and predisposes an individual to most psychiatric illnesses, including schizophrenia, bipolar disorder, and major depression. Treatments that aim at creating more adaptive understanding and response to stimuli reminiscent of these adverse experiences may be critical in ameliorating a diversity of mental disorders.

DISORDERS OF AMYGDALA ACTIVITY AND ITS REGULATION

Seminal preclinical work from the laboratories of scientists such as Joseph LeDoux, Gregory Quirk, and Michael Davis demonstrated over the past three decades that the amygdala, an almond-shaped collection of neurons in the limbic cortex, is at the hub of a network that mediates conditioned (Pavlovian) fear (Ciocchi et al., 2010; Davis, 1992; LeDoux, 2000; Milad & Quirk, 2002; Quirk, Garcia, & González-Lima, 2006; Rodrigues, Schafe, & LeDoux, 2004; Tye et al., 2011). In the classic experiment, a laboratory rodent is conditioned to respond with a freezing response to a tone as it normally does to a mild electric shock. The tone stimulus is relayed from the auditory thalamus to the central nucleus of the amygdala (CNA) and then to the lateral nucleus of the amygdala (LA). From there, information is sent to various effector regions that produce the characteristic fear responses of freezing: increased heart rate, ventilation, and blood pressure and increased production of glucocorticoids. Each step along this relay of fear information is mediated by gene activation and de novo protein synthesis. Particularly crucial for the fear response are glutamatergic neurons in the amygdala (Harvey & Shahid, 2012). Acquisition of conditioned fear can be inhibited by ablation of the amygdala, blocking gene expression or protein synthesis, or antagonism of glutamate neurotransmission. Stress causes dendritic growth in the amygdala, thereby increasing the number of synaptic connections

capable of mediating the fear response (Pillai et al., 2012). In other areas of the brain, such as prefrontal cortex, stress decreases dendritic arbor expansion (Gorman & Docherty, 2010). Within the amygdala itself, the ratio of neuronal propagation from the lateral nucleus to the central nucleus determines trait anxiety levels in rodents (Avrabos et al., 2013).

It has also been shown that extinction of the conditioned fear response requires intact pathways from the mPFC to the amygdala (Berkowitz, Coplan, Reddy, & Gorman, 2006; Quirk et al., 2006). Extinction also requires a well-characterized series of molecular events (Mamiya et al., 2009; Nader, Schafe, & LeDoux, 2000) and creates a memory that does not erase the conditioned fear memory but coexists with it (Bouton, 2002; Milad, Rauch, Pitman, & Quirk., 2006). Thus, the fear response is readily reactivated and must be reconsolidated to remain in permanent memory. Protein synthesis inhibitors can block reconsolidation of a reactivated fear memory and erase it (Hupbach, Gomez, Hardt, & Nadel, 2007; Milekic & Alberini, 2002). In humans, the beta-adrenergic receptor antagonist propranolol also blocks reconsolidation of fear (Kindt, Soeter, & Vervliet, 2009).

As this work was published, clinical scientists immediately wondered whether the molecular biology of conditioned fear bears any relationship to pathologic fear states in humans, such as panic attacks and phobias. A large body of brain imaging studies has now confirmed that, just as in laboratory animals, the connection between the amygdala and mPFC is inversely correlated with anxiety (Kim & Whalen, 2009; Kim et al., 2011; Phelps, Delgado, Nearing, & LeDoux, 2004). That is, the stronger the functional connection between the mPFC and the amygdala, the lower the level of anxiety in the individual. Furthermore, many brain imaging studies have shown that patients with anxiety disorders and with depression, both unipolar and bipolar, manifest exaggerated amygdala responses and/or volume (Davey, Allen, Harrison, & Yücel, 2011; Holmes et al., 2012; Kuo, Kaloupek, & Woodward, 2012; Lipka, Miltner, & Straube, 2011; Nitschke et al., 2009; Perlman et al., 2012; Tao et al., 2012; Versace et al., 2010). A postmortem study showed abnormal amygdala anatomy in suicide victims (Gos et al., 2010). Abnormal amygdala responses have even been seen in young children with depression (Gaffrey et al., 2011; Gaffrey, Barch, Singer, Shenoy, & Luy, 2013). Reduced mPFC responses and functional connectivity between the prefrontal cortex and the amygdala are also well reported in mood and anxiety disorders (Burghy et al., 2012; de Carvalho et al., 2010; Erk et al., 2010; Etkin, Prater, Schatzberg, Menon, & Greicius, 2009; Garakani et al., 2007; Kim et al., 2011; Kong et al., 2013; Milad et al., 2006, 2009; Moses-Kolko et al., 2010; Williams et al., 2006).

Disruptions in amgydala/mPFC function in anxiety and depression have led to insights into treatment of these conditions. Antidepressant medications that are effective in treating mood and anxiety disorders normalize amygdala responses (Faria et al., 2012; Ruhé, Booij, Verlman, Michel, & Schene, 2012; Sheline et al., 2001; Victor, Furey, Fromm, Öhman, & Drevets, 2010). Antidepressants also reduce fear responses in fear-conditioned rats (Burghardt, Sullivan, McEwen, Gorman, & LeDoux, 2004). However, just as they do in humans with panic disorder, antidepressants appear to interfere with extinction of conditioned fear (Barlow et al., 2000; Burghardt, Sigurdsson, Gorman, McEwen, & LeDoux, 2013). Reasoning that behavior therapy of phobias is analogous to extinction of conditioned fear, clinical studies have shown that glutamate analogues such as D-cycloserine enhance the therapeutic effect in patients just as they promote extinction in laboratory animals (Bouton, Vurbic, & Woods, 2008; Hoffman et al., 2006; Ressler et al., 2004). Dissociation between the anterior cingulate, a brain region closely associated with the mPFC, and the amygdala predicted treatment response to the experimental antidepressant agent ketamine (Salvadore et al., 2010). These findings may even apply to some aspects of psychoanalytic psychotherapy (Gorman & Roose, 2011).

The key here is that abnormalities in amygdala responses are common across a broad range of mood and anxiety disorders (Ressler & Mayberg, 2007). As Etkin and Schatzberg (2011) noted, "These data support the existence of a common abnormality in anxiety and depression in the ventral cingulate and the amygdala, which may be related to a shared genetic etiology." That anxiety disorders and depression share a common biology is no surprise given the high degree of comorbidity between them (Kessler, Ruscio, Shear, & Wittchen, 2010).

Focusing on the amygdala and its connection to the mPFC is, of course, a simplification of a highly complex neural network that involves many other brain regions, including the dorsolateral PFC, the

anterior cingulate cortex, the bed nucleus of the stria terminalis, the insula, and the hippocampus. As LeDoux (2014) and Berkowitz and colleagues (2006) have noted, unlike laboratory rodents, humans employ a whole set of higher-order cognitive functions that interact with the automatic functions embedded in the amygdala and its connections. As a result, LeDoux pointed out (2014), the expression of conditioned fear in a rodent and the experience of conscious fear in humans are not coterminous. Yet the basic premise holds true even when the complexity of neural function is considered: the fear pathways and molecules that are involved in fear and its extinction in laboratory animals are also involved in fear responses in humans and are disrupted across a broad range of mood and anxiety disorders. Although there are clearly differences in symptomatic presentation among patients with the various *DSM-5* types of anxiety and mood disorders, research suggests that they share at least one common biological underpinning.

DISORDERS OF THE CONNECTION BETWEEN THE ORBITOFRONTAL CORTEX AND THE VENTRAL STRIATUM

While progress in understanding brain circuits underlying anxiety and depression followed the pathway from preclinical to clinical brain imaging studies, the elucidation of a specific brain network underlying compulsive and obsessive symptoms ran in the opposite direction. In this case, the abnormal circuit activity runs from a region in the frontal cortex, the orbitofrontal cortex (OFC), to the ventral striatum. As Rauch and Carlezon (2013) noted, "Decades of functional brain imaging data indicate that in [obsessive-compulsive disorder], the nodes of this network exhibit hyperactivity at rest that is exacerbated during a symptom induction and attenuated by successful treatment."

For many years since the publication of the *DSM-III* in 1980 first laid out the modern categories of psychiatric diagnosis, many experts expressed the belief that obsessive-compulsive disorder (OCD) was incorrectly placed among the anxiety disorders (Stein et al., 2010). Indeed, in *DSM-5*, OCD is no longer included in the anxiety disorders but is instead in its own category with several other conditions that involve repetitive behaviors. Almost from the beginning of the application of modern brain imaging technologies to mental disorders, investigators studied patients with OCD. More than 15 years ago Saxena, Brody, Schwartz, and Baxter (1998) were able to assemble a literature search of brain imaging studies involving patients with OCD and reported a general finding of hyperactivity in pathways from the OFC to the striatum. Since then several studies and excellent reviews have appeared, all pointing to the same abnormally regulated brain network (Chamberlain et al., 2008; Milad & Rauch, 2012; Saxena & Rauch, 2000; Whiteside, Port, & Abramowitz, 2004).

Once again, dysfunction in this circuit is not limited to a single *DSM* category of illness but appears to occur in many situations in which there is a failure to regulate behavior or thoughts, such as eating disorders, tics and Tourette syndrome, and substance abuse (Marsh, Maia, & Peterson, 2009a; Marsh et al., 2009b). Thus, the brain region–specific abnormalities adhere to a set of abnormal symptoms and behaviors that cut across multiple categories of illness.

Only much more recently, however, have elegant animal studies elucidated the nature of the abnormalities in this circuit. Mice with a deletion of the SAP90/PSD95-associated protein 3 (SAPAP3) gene, which is highly expressed in the striatum, were shown to exhibit marked compulsive grooming behaviors (Welch et al., 2007). Further study of these mice revealed abnormalities in corticostriatal synapses (Yang & Lu, 2011). Most recently, two elegant studies have provided important corroboration of the clinical imaging findings. Ahmari and colleagues (2013) used the technique of optogenetics, which enables direct stimulation of light-sensitive neurons in a specific brain pathway, to stimulate glutamatergic neurons in the projections from the OFC to the ventromedial striatum in mouse brain. Repeated stimulation of these neurons led to compulsive grooming behavior. Burguière, Monteiro, Feng, and Graybiel (2013) obtained direct electrophysiologic recordings from the OFC and striatum in the *Sapap3* mutant mice. They found that the excessive grooming behavior in these mice was directly related to a failure to inhibit neurons in the striatum. Next they showed that optogenetic stimulation of the mouse OFC restored normal inhibition to the striatal neurons and blocked excessive grooming. Thus, the Ahmari and the Burguière studies documented that compulsive behavior in the mouse is under the direct control of the OFC–striatal pathway, the same pathway that has been shown to

be dysfunctional in humans who display abnormal repetitive thoughts and behaviors.

Once again we must acknowledge that we have simplified the anatomy involved in these circuits. Human imaging studies in patients with OCD and other compulsive behavior–related disorders reveal the involvement of other brain regions, including the thalamus and the anterior cingulate. Furthermore, to the degree that the competitive behaviors in these disorders are responses to fear, the mPFC and amygdala are apparently invoked as well. Nevertheless, we once again have strong evidence that specific abnormalities in specific brain circuits are involved in a type of symptomatic presentation. This, we hope, will translate into treatments that attempt to restore OFC control over glutamate neurons in the ventral striatum. For example, knowledge of the neurocircuitry involved in OCD has led to studies of deep brain stimulation in patients whose conditions are refractory to medication and psychotherapeutic interventions. These studies, in which electrodes are implanted directly into structures within these pathways, have been reported to be successful in small pilot trials (Rauch et al., 2006).

Positive Symptoms of Psychosis and Enhanced Dopamine Transmission in the Striatum

The discovery in the 1950s and 1960s that newly developed medications capable of relieving psychotic symptoms in patients with schizophrenia all had the property of blocking the ability of dopamine to bind to its receptor sites in the central nervous system led to the "dopamine hypothesis" of schizophrenia (Eyles, Felder, & Meyer, 2012; Lau, Wang, Hsu, & Liu, 2013; Madras, 2013). According to this hypothesis, the "cause" of schizophrenia is an excess amount of dopamine in the brain. Just as was the case for the "serotonergic" and "noradrenergic" hypotheses of mood and anxiety disorders, this idea is based on the logic that if a drug works in patients with an illness (proposition A) and the drug targets a specific neurotransmitter system (proposition B), then the illness must be the result of an abnormality in that neurotransmitter system (conclusion C).

Patients with schizophrenia are indeed more behaviorally sensitive to the effects of dopamine agonists such as amphetamine than healthy controls (Seeman, 2013). Nevertheless, it eventually became apparent that the antipsychotic drugs that block the D_2 receptor are effective in treating only one aspect of schizophrenia, the so-called positive psychotic symptoms (hallucinations, delusions, thought disorder), and do not ameliorate the protean negative, cognitive, or affective symptoms of the disorder. Moreover, cognitive symptoms seem to predate positive symptoms in patients with schizophrenia and to be more closely related to long-term function. Thus, schizophrenia is increasingly referred to as a cognitive disorder (Kahn & Keefe, 2013) and the dopaminergic hypothesis disparaged. Propositions A and B may both be true to some extent, but they are not sufficient to reach conclusion C.

There is no question that inferring causality from the mechanism of action of a drug in the central nervous system is a perilous undertaking. The dopaminergic hypothesis now seems naïve. But it is also the case that abundant research has confirmed that excessive dopaminergic activity in the striatum is a reliable accompaniment of a specific and well-characterized set of symptoms. The problem is that these symptoms do not restrict themselves to a single *DSM-5* condition and therefore do not explain any single class of disorder. Rather, "hyperdopaminergic" neurotransmission is almost certainly present in the striatum of patients experiencing positive psychotic symptoms, regardless of whether the patient has been diagnosed with schizophrenia, bipolar mania, or amphetamine-induced psychosis. An extensive series of studies in the past 30 years have shown that when a patient hears voices and develops paranoid delusions, it is very likely that the dopamine pathways in the mesolimbic pathway that culminate in the striatum are hyperactive and that any medication that blocks the D_2 receptor will alleviate those symptoms.

To be sure, the animal models derived from the dopaminergic hypothesis of schizophrenia were never entirely satisfying, largely because it is nearly impossible to grasp what positive psychotic symptoms, let alone the full syndrome of schizophrenia, would entail in a rodent. Most of these models involved administering dopamine agonists such as apomorphine and amphetamine to rats and measuring subsequently elevated levels of locomotor hyperactivity and stereotypy (Geyer & Moghaddam, 2002; Jones, Watson, & Fone, 2011). Not surprisingly, these responses could be blocked by antipsychotic drugs that restrict access of dopamine agonists to the D_2 receptor. Perhaps more encouraging was the finding that dopamine agonists produced the

same abnormalities in the prepulse inhibition (PPI) test in rodents as are seen both in unmedicated patients with schizophrenia and in healthy controls given amphetamine and that these abnormalities in the sensory gating paradigm could also be blocked by antipsychotic medications, including the second-generation antipsychotics (Braff, 2010; Powell, Zhou, & Geyer, 2009).

It is at the level of functional imaging studies in patients with schizophrenia, some using remarkably clever methods to measure in vivo dopamine activity, that the association between hyperdopaminergic function and psychotic symptoms has been clearly elucidated. Studies using positron emission tomography (PET) and single photon emission computed tomography (SPECT) demonstrate excess release of dopamine by neurons in the ventral striatum and consequent alterations in D_2 receptor number and function in both medicated and unmedicated patients with schizophrenia (Brunelin, Fecteau, & Suaud-Chagny, 2013; Laruelle, 1998; Laruelle & Abi-Dargham, 1999; McGowan, Lawrence, Sales, Quested, & Grasby, 2004). In a series of studies using a novel approach, Abi-Dargham, Laruelle, and colleagues administered the dopamine-depleting agent alpha-methyl-para-tyrosine (AMPT) to healthy controls and antipsychotic drug–naïve patients with schizophrenia, thus enabling them to create a true baseline state (Abi-Dargham, van de Giessen, Slifstein, Kegeles, & Laruelle, 2009). Using SPECT imaging of D_2 receptors they once again showed increased dopamine release in the patients compared to the controls. These findings relate most closely to untreated patients with positive psychotic symptoms and predict favorable response to antipsychotic medications (Miyake, 2011).

In terms of antipsychotic effects, imaging studies have shown that there is a tight correlation between medication efficacy and D_2 receptor binding and that approximately 65% of available D_2 receptors must be blocked for a drug to have antipsychotic effects (Kapur, Zipursky, Jones, Remington, & Houle, 2000; Tauscher & Kapur, 2001; Yilmaz et al., 2012). At 80% D_2 receptor occupancy, however, extrapyramidal symptoms emerge as a significant clinical limitation of antipsychotic drugs (Kapur, 1998; Stone, Davis, Leucht, & Pilowsky, 2009). Thus, because second-generation antipsychotic drugs are more likely to remain within this narrow therapeutic window than first-generation ones, they are less likely to cause extrapyramidal symptoms at therapeutic doses (Howes et al., 2009; Kapur & Mamo, 2003). Understanding the role of dopamine and the D_2 receptor in the genesis of positive psychotic symptoms has therefore led to important insights into the mechanism of action of antipsychotic drugs and created a pathway for developing better treatments.

Unfortunately, far fewer brain imaging studies evaluating dopamine neurotransmission in patients with bipolar disorder than with schizophrenia have been published. Performing brain imaging studies on patients in an acute manic state is plainly a Herculean task. Nevertheless, available studies suggest excessive mesolimbic dopamine activity (Anand et al., 2000, 2011; Cousins, Butts, & Young, 2009). Of note, Pearlson and colleagues (1995) used PET scanning to show that elevated D_2 receptor numbers were more closely associated with psychotic than mood symptoms in bipolar patients. The same conclusion was reached by Gonul, Coburn, and Kula (2009) in their review of imaging studies involving bipolar patients.

We have then a solid and well-replicated set of findings linking a specific disturbance in a neurotransmitter (dopamine) in a specific brain region (ventral striatum) to a specific set of psychiatric symptoms (positive psychotic symptoms). Furthermore, these findings explain the mechanism of action of a therapeutic intervention (antipsychotic drugs). There is no question that this represents only the tip of the iceberg in terms of what is wrong with patients with schizophrenia, bipolar disorder, and addiction to psychostimulant drugs. Nevertheless, it represents a coherent and important story that belies the notion that translational neuroscience research has ubiquitously failed to reveal fundamental aspects of psychopathology.

Substance Abuse Causes Sensitization of the Ventral Tegmental Area–Nucleus Accumbens Dopamine Pathway

Nora Volkow, the director of the National Institute on Drug Abuse, recently pointed out that "all drugs of abuse increase dopamine, which is crucial for their effect" (Levin, 2013). In so stating, Volkow referred to her own work as well as a multitude of others showing that drugs of abuse cause the same biological changes in laboratory animals and humans. What may be most remarkable about these findings is that they apply to almost all abused substances—alcohol, nicotine,

stimulants, and opiates—even though each has its own chemistry and receptor targets in the brain.

Volkow has been at the forefront of research using brain imaging to show the central role played by the brain's so-called reward pathway in all forms of drug addiction. This circuit, also called the mesolimbic pathway, comprises dopaminergic neurons that originate in the VTA of the midbrain and project to striatal areas, most prominently the NA. Many forms of rewarding experiences stimulate activity via the VTA–NA pathway, and rats will press levers to obtain stimulation of this pathway. Similarly, alcohol, cocaine, heroin, and nicotine—almost all addictive substances—activate the VTA–NA dopamine neurons, producing a pleasurable feeling at first (Gardner, 2011; Hou, Tian, & Zhang, 2012; Ross & Peselow, 2009; Volkow, Wang, Fowler, Tomasi, & Telang, 2011). Although heroin, for example, is an opioid and therefore targets the brain's opiate receptors, it causes a powerful release of dopamine from nerve terminals in the VTA–NA pathway (Hou et al., 2012). Animal studies and brain imaging studies in humans converge to show that dopamine levels are indeed increased in the VTA–NA circuit after addictive drug ingestion (Feltenstein & See, 2008). For a variety of reasons, only some of which are currently clear (e.g., exposure to high levels of stress, family history of substance abuse), a percentage of individuals become obsessed with these substances and dependent on their effects on the dopamine pathway. These individuals, both animal and human, begin taking the substance repeatedly.

Animal and clinical studies have both shown that repeated administration of addictive substances induces a reduction in availability of dopamine and its receptors in the VTA–NA pathway (Gardner et al., 2011; Maldonado, 2003; Weiss, Markou, Lorang, & Koob, 1992). In monkeys addicted to cocaine, the lower the number of available D_2 receptors, the greater the rates of cocaine self-administration (Nader et al., 2006). PET studies have shown that reduction in dopamine function is also the case in human addicts (Martinez et al., 2012; Volkow, Fowler, Wang, Swanson, & Telang, 2007). Alcoholics, for example, show reduced dopamine response when given the dopamine agonist methylphenidate as compared to control subjects during PET scanning (Volkow et al., 2013). The VTA–NA circuit is weaker the longer a person has been addicted to cocaine (Gu et al., 2010). This makes it imperative that the addict either take greater amounts of the abused substance more frequently to obtain consistent effects or succumb to the highly dysphoric symptoms of withdrawal.

The molecular mechanisms by which addictive substances produce alterations in neuronal responsiveness in the VTA–NA pathway are rapidly becoming clear. Eric Nestler, among others, has shown that repeated administration of most addictive substances leads to predictable changes in gene expression, mediated in part by epigenetic effects. Within the NA, the genes encoding several proteins, including sirtuins (Ferguson et al., 2013), transcription factors like ΔFosB, and growth factors like brain-derived neurotrophic factor (BDNF), are activated by drug administration (Bilinski et al., 2012; Kelz et al., 1999; McCarthy, Brown, & Bhide, 2012; McGinty, Whitfield, & Berglind, 2010; Nestler, 2012; Nestler, Barrot, & Self, 2001; Schmidt et al., 2012). These changes in gene expression are mediated by drug-induced epigenetic alterations in the acetylation and methylation of histones and DNA (see below for further explanation) (Maze & Russo, 2010; Nestler, 2013).

As is the case with the other three examples of neurobiological progress in understanding mental illness discussed so far, the VTA–NA dopamine story for drug addiction has complexities and limitations. This pathway is, of course, highly interconnected with many other brain networks and is influenced by a host of other neurotransmitters besides dopamine. And despite the fact that the biology of drug addiction's effects on dopamine in the mesolimbic pathway is quite extensively confirmed, it has not yielded clinical interventions yet. Nevertheless the findings are quite remarkable for their consistency across multiple substances and multiple species. Substances whose primary molecular targets in the brain are highly divergent are involved: nicotine, which targets the acetylcholine receptor; heroin and narcotic analgesics such as oxycodone, which target the endorphin system; cocaine and methylphenidate, which target the dopamine transporter protein; and alcohol, which targets multiple brain systems, especially GABA and benzodiazepine receptors. All of these have in common acute stimulation and chronic downregulation of the dopamine "reward" pathway, whether these phenomena are looked at with magnetic resonance imaging (MRI) and PET scans in humans or microdialysis and electrophysiologic recording in laboratory animals. The underlying genetic and epigenetic

changes that underpin addiction, craving, and withdrawal are elegantly understood. Clearly, understanding the biology of drug addiction has been, and will likely continue to be, one of the triumphs of translational research from basic to clinical science in our understanding of mental illness. Furthermore, this understanding will help guide the development of both psychotherapeutic and somatic interventions. It will be critical to understand, for example, which of the many psychosocial interventions now employed to treat addiction affect the VTA–NA pathway and whether positive response is correlated with changes in activity. This kind of work can now be easily done with available neuroimaging techniques. Direct stimulation of the VTA–NA pathway with deep brain stimulation is also being explored as a treatment option (Arulpragasam et al., 2013).

Adverse Early Life Experiences Increase Risk for Most Mental Disorders

The four examples discussed thus far in this section highlight instances in which preclinical research and clinical research are synchronous in identifying discrete abnormalities in brain function that are consistently associated with specific psychiatric symptoms and/or behaviors. They do not tell us, however, why some individuals have these abnormalities and others do not. For most of the latter half of the twentieth century the prevailing belief among scientists was that the reasons for these differences among people rested in variations in the genome.

When medications for psychiatric illnesses were introduced in the late 1950s, the dominant school of thought about psychopathology was psychoanalysis. Although Freud occasionally mentioned "constitutive" factors to explain the genesis of mental illness, psychoanalysis relies mainly on the effects of early life events, primarily interactions with parents, as the determinants of later behavioral and emotional abnormalities. But then psychopharmacologists, flushed with the success of new antidepressants and antipsychotics in clinical practice, pointed out that the newly employed medications worked regardless of an individual patient's life experiences and therefore downplayed the significance of adverse life events in the pathogenesis of mental disturbances. Cognitive-behavioral therapy also deals mainly with current symptoms rather than historical events and therefore supports the idea that early life adversity is not a major factor, at least in the successful treatment of a psychiatric illness. These ideas quickly attracted the attention of mental health advocacy groups, who had long been burdened with nonsensical labels like the "schizophrenogenic mother." When *DSM-III* revolutionized the system of psychiatric diagnosis in 1980, it included only one disorder with clear ties to life events: posttraumatic stress disorder (PTSD). In this case alone was it acknowledged that extreme traumatic events could be the proximate cause of a psychiatric syndrome.

An enormous amount of research has thus been conducted attempting to locate the genetic basis of mental disorders. There is absolutely no doubt that many disorders are indeed heavily influenced by inherited factors. Family, twin, and adoption studies clearly show that as much as 50% to 60% of the variance in whether one gets a psychiatric illness is attributable to heritable factors. Because these conditions are not inherited according to the principles of simple Mendelian genetics (i.e., mutations in discrete dominant and recessive genes), the search for the complex, multigenetic causes of mental illness has been difficult. So far, we have many promising leads for mutations in genes that predispose to specific psychiatric illnesses. There is little doubt that as genetic techniques continue to advance, more and more specific genetic signatures for psychiatric illness will be found. However, current evidence suggests that there is considerable overlap among *DSM* categories of illness in abnormal genetic markers (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Once again, it is likely that our current notion of such categories will be eroded and rearranged as more information is forthcoming for genetic research.

At the same time, however, there has been a remarkable revival in more recent years of investigation into experiential causes of mental disorders. This work has led to clear preclinical and clinical evidence that early life adversity, working through well-defined biological mechanisms, predisposes an individual to later development of a mental disorder. Much of the recent work linking early life adversity to psychopathology involves the long-term effects of child abuse, which has been shown to increase the risk of a range of disorders, including conduct disorder, antisocial personality disorder, anxiety disorders, substance use disorder, and depression (Heim & Nemeroff, 2001; Kessler, Davis, & Kendler, 1997; McLaughlin et al.,

2010; Withers, Tarasoff, & Stewart, 2013; Young, Abelson, Curtis, & Nesse, 1997). Childhood maltreatment is associated with long-lived structural and functional abnormalities in brain regions such as the amygdala and anterior cingulate (Dannlowski et al., 2012; McCrory, De Brito, & Viding, 2012). But dramatic and obvious forms of early life trauma may not be required for there to be stress-related effects on the brain. Studies have even reported that urban dwelling and urban upbringing, both linked to adverse mental health outcomes, are linked to changes in activity of the amygdala and anterior cingulate cortex (Lederbogen et al., 2011; McKenzie, Murray, & Booth, 2013).

Perhaps even more striking are the mounting data that childhood adversity also predisposes to psychotic illnesses (Kelleher et al., 2013; Stilo & Murray, 2010; Varese et al., 2012). Murray and colleagues have shown that childhood immigrant status is a significant risk factor for developing schizophrenia and that this effect cannot be accounted for by familial or genetic factors alone (McDonald & Murray, 2000). Importantly, valid and reliable methods for assessing childhood adversity have been developed for research into schizophrenia and other disorders (Brown, Craig, Harris, Handley, & Harvey, 2007). Thus, a condition that has in recent years been thought to be purely caused by abnormal genes and physical prenatal insults (e.g., infection and malnutrition of pregnant women) now seems clearly to have early life stress as a component of its etiology.

The work demonstrating that early life adversity is an important risk factor for developing mental disorders is reflected in an abundance of preclinical studies in which adverse rearing produces permanent changes in gene expression, brain structure and function, and behavior into adulthood (Rinaman, Banihashemi, & Koehnle, 2011). Michael Meaney, Paul Plotsky, and many others have shown that adverse early rearing experiences in mice and other rodents lead both to long-lived fearful behaviors and discrete biological changes, including pronounced and permanent effects on the regulation of glucocorticoids and other stress hormones (Caldji et al., 1998; Caldji, Diorio, & Meaney, 2000; Liu et al., 1997). Neonatal isolation stress even increases self-administration of cocaine in adult rats (Kosten, Miserendino, & Kehoe, 2000). In a series of experiments with the bonnet macaque nonhuman primate, Rosenbaum, Coplan, and colleagues found that a type of adverse rearing experience during infancy called variable foraging demand results in fearfulness and elevated levels of the stress hormone corticotropin-releasing hormone in the cerebrospinal fluid of adult animals (Coplan et al., 1996). Just as early life stress predisposes rats to a life of anxiety-like behavior, so does enriched early life experience reduce such behaviors (Baldini et al., 2013; Francis, Diorio, Plotsky, & Meaney, 2002).

An exciting line of investigation has shown that early life adversity produces longstanding changes in the epigenetic regulation of gene expression. Maternal care affects the expression of genes encoding proteins such as corticotropin-releasing factor and oxytocin that regulate emotion and behavior in adult offspring (Meaney, 2001). These changes in gene expression occur because of alterations in levels of DNA methylation and acetylation, which generally suppress and enhance gene expression, respectively (Weaver et al., 2004). Nestler's group subjected mice to both social defeat stress and social isolation, both of which lead to depressive-like behaviors. They showed that both maneuvers increase methylation of histones, the proteins that are packaged with DNA in the cell nucleus, in the NA, thus repressing the expression of several genes (Wilkinson et al., 2009). This effect of stress on methylation is reversed by treatment with the antidepressant imipramine. Earlier, the group had shown that imipramine reverses histone methylation and downregulation of gene expression by increasing histone acetylation of promoter regions of genes, like those encoding the transcription factor BDNF (Tsankova et al., 2006). Findings like these raise the possibility that inhibitors of histone deacetylase (HDAC), which increase gene expression by enhancing acetylation, may be useful antidepressant medications (Covington et al., 2009). Changes in methylation of histones and therefore gene expression produced by early life stress in laboratory animals are persistent and associated with behavioral changes throughout the life of laboratory animals (Murgatroyd et al., 2009). In the monkeys raised under the variable foraging demand condition mentioned above, animals with greater DNA methylation of the gene encoding the serotonin reuptake protein (5-HTT), the molecular target of many antidepressant medications, were most at risk for later behavioral abnormalities (Kinnally et al., 2011). Similarly, surrogate-peer–reared rhesus monkeys demonstrate differential DNA methylation in prefrontal cortex and peripheral cells into adulthood compared with maternal-reared animals

(Provençal et al., 2012). Stress produces enduring changes in DNA methylation in humans as well as rodents (Ursini et al., 2011). Differences in histone acetylation have been reported in young patients with schizophrenia compared to age-matched controls (Tang, Dean, & Thomas, 2011).

Thus there is now abundant evidence that early life experience operates through a set of well-defined changes in brain structure, function, and gene expression to determine emotions and behaviors throughout life. Evidence for this is found in both preclinical and clinical studies that identify the same brain circuits as affected by early life adversity. The story continues in the laboratory, where the mechanism for these effects—epigenetic control of gene expression—is beginning to unfold. In the laboratory, both altering experience and administering medications can reverse many of these changes, even in adult animals many years remote from the original early life adversity. This raises the expectation that psychotherapy and medications will similarly be shown to work through disordered neural circuits and abnormally expressed genes to ameliorate psychiatric disorders that have been caused, at least in part, by exposure to traumatic life events.

Implications

We conclude that scientists and clinicians should take heart in the amazing amount of progress that has been made since 1980, when *DSM-III* was published, in understanding the neurobiological basis of mental illness. These findings will likely result in wholesale revisions of our diagnostic nomenclature. We cannot yet point to an array of new treatments directly based on recent advances in basic and clinical neuroscience, but progress is being made. For one thing, it is important to know whether nonmedication interventions produce observable changes in human brains and whether these changes are correlated with symptomatic response. We have cited some examples of this being the case with respect to psychotherapy for mood and anxiety disorders. More such information will help define which interventions are most effective for which specific set of symptoms and for which individual patients and will inevitably lead to refinements of current treatment approaches and the development of new ones. On the somatic side, although it is too early to tell whether it will prove clinically useful, the convergence of basic and clinical research has brought about the exciting new trials of the anti-glutamatergic anesthetic ketamine as a rapid-onset treatment for depression. Directly stimulating specific malfunctioning brain circuits with deep brain stimulation is another example in which biology is guiding the development of therapy. It is therefore critically important that research follow the concordance of laboratory and clinical evidence in making diagnostic categories rather than the current practice of trying to make the science fit into our preexisting categories of illness. This approach should go a long way in sharpening our ability to develop therapeutic interventions that target specific clusters of symptoms and offer our patients meaningful relief.

BIG PHARMA: DIAGNOSIS AND TREATMENT

The subtitle of Allen Frances's *Saving Normal* ("An Insider's Revolt against Out-of-Control Psychiatric Diagnosis, *DSM-5*, Big Pharma, and the Medicalization of Ordinary Life") targets his principal *DSM-5* targets. The material in the preceding section of this chapter questions the pessimism with which Frances and others in psychiatry view the potential of neuroscience research to yield important diagnostic payoffs. By contrast, the insistent criticisms of the role of the pharmaceutical industry in skewing diagnostic and treatment practices in psychiatry, as examined here, seems appropriately placed.

Here is a quote from Frances (2013) in what he scathingly calls "Big Pharma":

> Big Pharma is really big and incredibly successful. Worldwide sales exceed $700 billion each year. . . and the profit margin, at a whopping 17 percent, is among the highest of any industry. Why so big and so successful? The companies justify their high prices and enormous returns by touting their research effort to advance medical science and improve patient care. This is mostly fluff. Pharma spends twice as much money ($60 billion) on promotion as on research. (p. 90)

The coin of the realm for demonstrating clinical efficacy of any new treatment, whether for a mental disorder or a medical illness, is the double-blind, randomized, controlled trial, also known as the RCT. Among other touted virtues, this methodology is

believed to be foolproof against investigator bias. If the scientists conducting a trial do not know whether a research subject is being administered the investigational intervention or a placebo, then biased assessment of outcome should be rendered impossible.

Much, of course, has been written about the ways in which the RCT can fall short of this lofty expectation. It is said to be harder to conduct a blinded trial when psychotherapy is the active intervention than when it is a medication because of the difficulty designing credible placebo psychotherapies. Double blinds in medication trials, however, are sometimes easily broken when an active medication has recognizable adverse side effects not shared by the supposedly matched placebo. Also, only a small subset of patients with any diagnosis actually turn out to meet the inclusion criteria for most RCTs, making generalizability suspect.

None of these potential shortcomings of RCTs arouse the level of fervor, however, that the issue of pharmaceutical company funding generates. Because there is generally no commercial source of funding for studies of psychosocial interventions, they are believed to be less prone to biased assessment. While that is unlikely to be entirely the case—partisans of one type of psychotherapy over another may have a financial stake in a study's outcome and may even decide to withhold publication of a negative finding that does not support their favored intervention—it is clearly the case that studies of medication interventions are far more susceptible to financial pressures and biases.

It is now well documented that drug trials funded by pharmaceutical companies are more likely to report positive findings than those funded by other sources such as federal or nonprofit organization grants (Bekelman, Li, & Gross, 2003; Kelly Jr. et al., 2006; Lundh, Sismondo, Lexchin, Busuioc, & Bero, 2012; Perlis et al., 2005). Part of this problem stems from the unwillingness of drug companies to publish papers reporting negative results of trials involving their proprietary products. Such publication bias can have a profound effect on the impression we have of whether a drug actually makes a clinically meaningful difference (Koesters, Guaiana, Cipriani, Becker, & Barbui, 2013). Mandated registries of clinical trials that make negative results publicly available are designed to ameliorate this problem (Turner, 2013), but it is not yet clear whether they successfully address publication bias and balance the picture. We do not know whether scientists, clinicians, journal editors, or the public actually consult these registries when making decisions about the relative validity of results promulgated by the pharmaceutical industry.

There are many ways besides publication bias that industry funding can distort our understanding of a drug's true risks and benefits. For example, a recent study found that antidepressant drugs under investigation made by a study sponsor were given at higher doses than comparison drugs and that higher dosing was associated with better outcomes (Sinyor et al., 2012). Thus, at the earliest stages of study design, the funding source can bias study outcomes even when the design appears to be a perfectly respectable RCT.

It is also claimed that industry distorts the recommendations and decisions made by committees and organizations charged with producing practice guidelines and diagnostic systems. Cosgrove, Bursztajn, Krimsky, Anaya, and Walker (2009) reported that 95% of the members of three American Psychiatric Association Clinical Practice Guideline committees had financial ties to drug companies that make medications recommended in the guidelines. One criticism of *DSM-IV* was that a high percentage of panel members had relationships with the pharmaceutical industry (Cosgrove, Krimsky, Vijayaraghavan, & Schneider, 2006). This led to a disclosure policy of such relationships for *DSM-5* panel members. Nevertheless, Cosgrove and Krimsky (2012) found that there was no reduction in financial conflicts of interest between *DSM-IV* and *DSM-5*. How these potential conflicts of interest actually affect clinical care is unclear, especially considering that psychiatric diagnosis appears not to be the guiding factor in most decisions about what treatment to employ: A recent study found that a majority of people who take psychotropic medications had not received a specific psychiatric diagnosis (Wiechers, Leslie, & Rosenheck, 2013). Ties between industry and members of guideline and expert panels are not limited to psychiatry and appear to be ubiquitous throughout medicine (Moynihan et al., 2013).

Implications

There is currently a significant diminution in development efforts of psychotropic medications among major pharmaceutical companies. This stems from several factors, including the fact that many of the

"second-generation" antidepressants and antipsychotics are now off patent, making it difficult for drug companies to get newer, more expensive medications onto pharmacy formularies. An equally important factor is the low success rate of psychotropic medication development programs: Psychiatric drugs take longer to develop and have higher rates of failure than almost all other classes of medication (Sanders, 2013). Several large, prominent pharmaceutical companies have recently announced they are abandoning psychiatric drug development, further threatening hope that drugs for mental illness with substantially better efficacy and a reduced adverse side effect burden will be discovered. We are faced with the dilemma, then, of wanting to place more regulations on the conduct of clinical trials of psychotropic medications to reduce industry-related bias while at the same time wishing to spur development of breakthrough medications with novel mechanisms of action. As we grapple in this book with adjudicating which treatments for mental disorders are most effective, it is important to temper this latter wish with a sober recognition that currently available pharmaceutical industry–funded clinical trials of psychotropic drugs and expert recommendations about them are prone to significant conflicts of interest and subject to a variety of types of bias.

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2

Evidence-Informed, Culture-Based Interventions and Best Practices in American Indian and Alaska Native Communities

R. Dale Walker
Douglas A. Bigelow

In this chapter, we provide information and advice to audiences at the practice, program management, and governance levels concerned with "evidence-based programs and practices" (EBP) in Native communities. While blending all sources of best practices to yield continuously improving best practices is our primary purpose, we emphasize a defense of culture-based knowledge and practice because the systematic attempt to impose an EBP mandate on providers of behavioral health services in Native communities has not been an incentive to incorporate scientifically tested information about interventions. The approach we recommend, on the other hand, respects and accommodates culture-based knowledge, ways of knowing, and practice in Native communities, while facilitating the uptake of science-based knowledge. We describe several entrées to collaboration with Native communities: understanding and appreciating Native culture, knowledge, and healing practices; a logic model, used to frame our descriptions of evidence-informed culture-based interventions in a science-friendly fashion; the concept of "culture-as-treatment" and "cultural renaissance;" and some researchable theories of action underlying traditional healing strategy and techniques. We identify a means, compatible with local culture and context, of accelerating evidence-informed culture-based interventions: kernels. In a larger sense, our approach has relevance to any special population, whether indigenous, inner city, impoverished, homeless, or elderly.

INTRODUCTION

The One Sky Center (R. Dale Walker, MD, director) has sought out and promoted best practices in mental health, suicide, substance abuse, violence, and other behavioral health prevention and treatment practices and programs. Our population of interest is "aboriginal," "indigenous," "first nations" people worldwide, with a focus on Native (North) Americans, especially American Indians and Alaska Natives (AI/AN).[1] The Center has partnered with a number of other AI/AN academic, technical assistance, and governmental groups in projects ranging from local initiatives to broad multisite multiprogram initiatives. We have worked with individuals including horse whisperers, medicine persons, Indian health professionals, and politicians.

In this chapter, we share some of what we have learned about collaborative work striving toward best practice in AI/AN communities.[2] We have tried to

meet the very different needs for information and advice of several audiences: professionally trained clinicians who wish to practice EBP[3] in AI/AN communities; program leaders in AI/AN communities who wish to introduce EBP into their services; regulators, funders, and policymakers who wish to advance EBP in AI/AN communities; and social and behavioral scientists studying what works and how. The common, overarching purpose is continuously improving best practices for the purpose of better behavioral health and quality of life in Native Communities.

Throughout we have raised the profile of culture in the blend of sources of best practices.[4] While blending all sources of best practices is our primary purpose, we emphasize a defense of culture-based knowledge and practice for an important reason. There has been a systematic attempt to impose an EBP mandate on providers of AI/AN behavioral health services. This imposition is not an incentive to incorporate scientifically tested information about interventions (which we advocate) but rather a requirement that tribal programs be replications of programs drawn from an official list of model programs,[5] implemented with the assistance of the program developer, and subjected to fidelity testing to prove the protocols are implemented as originally designed and tested (which we oppose). In general, this mandate runs into a serious threat to external validity and challenges us to better understand science and its application.

The special problems for AI/AN communities with the EBP mandate are that model programs are especially difficult to generalize to Indian communities from the unique sites in which they were developed and evaluated. Developer training and fidelity testing are alien processes, and the loss of familiar and accepted practices can be traumatic for the tribe. Even if a model program were chosen, the personnel, training, and testing capacity to implement are rarely available. Finally, the very mandate, per se, is in conflict with principles of sovereignty and consultation.[6] However well intentioned, the EBP mandate is actually oppressive, disempowering, and a bad fit for AI/AN communities: a recipe for exacerbating, not ameliorating, health disparities. The approach we recommend, on the other hand, respects and accommodates culture-based knowledge, ways of knowing, and practice in AI/AN communities, while facilitating the uptake of science-based knowledge (Walker & Bigelow, 2011). We name this blend *evidence-informed culture-based interventions* and *tribal best practices*.

In merging epistemologically differing bodies of knowledge, it is helpful to identify underlying commonality. Different cultures use different ways of implementing healing, but there are fundamental commonalities. Behavioral treatments or ways of healing—psychiatric, psychological, social, and traditional—include changing expectancies, persuasion, motivation, education, personal narrative construction, storytelling, using placebo (mind–body) effects, diet, exercise, training/practice, and drugs. These largely face-to-face interventions rely upon healer characteristics and performance that are culture-specific, phenotypically, but, more fundamentally, generate trust, belief, hope, and expectation, which are essential to the effectiveness of such face-to-face interventions. Some contextual or environmental healing interventions depend upon vision, organization, and leadership. From this set of common treatment/healing fundamentals, we venture into our examination of behavioral health services in AI/AN communities.

The first place to look for science-based behavioral health programming applicable to an AI/AN target population are the EBP model program lists that have searchable databases with "American Indian/Alaska Natives" as a search criterion (e.g., Coalition for Evidence Based Policy, 2012; Community Preventative Services Task Force, 2013; National Indian Health Board, 2009; Office of Juvenile Justice and Delinquency Prevention, n.d.; One Sky Center, n.d.; Substance Abuse and Mental Health Services Administration [SAMHSA], n.d.c; University of Colorado, Institute of Behavioral Science, Center for the Study and Prevention of Violence, 2013). For example, the SAMHSA National Registry of Evidence-based Programs and Practices (NREPP) lists 323 interventions, 107 of which are identified as including 50% or more AI/AN subjects in the evaluation(s), and, of those, 83 are classified as having been evaluated using an "experimental" study design (SAMHSA, 2013).[7] These model programs are presumed by many to be synonymous with "scientific-evidence–based" interventions.

A few of those model programs have been tested in AI/AN communities (Chaffin, Bard, BigFoot, & Maher, 2012; Harper & Hornbuckle, n.d.); a few have been adapted for AI/AN communities (BigFoot & Braden, 2007; BigFoot & Funderburk, n.d.; BigFoot & Schmidt, 2010; Dionne, Davis, Sheeber, & Madrigal, 2009); and a few cross-walks between EBP and

culture-based interventions have been described. Many culture-based AI/AN behavioral health prevention and treatment practices and programs have been described (e.g., Echo-Hawk, 2011), but few would be categorized as EBP, and even fewer at a type 1 level of evidence (Yellow Horse & Yellow Horse Brave Heart, 2005).

Indeed, notably few scientific studies of practices and programs in Indian Country are reported in the literature or collected on lists of EBPs (Bartgis & Bigfoot, 2010; Del Grosso, Kleinman, Esposito, Martin, & Paulsell, 2012; Gone & Alcantara, 2007; Gone & Calf Looking, 2011). Among the culture-based interventions in AI/AN communities that have been listed, few have been developed, evaluated, and recognized as EBPs. One that has is Project Venture (Native Indian Youth Leadership Program, 2008; SAMHSA, n.d.e). Like Gone and Alcantara (2007) and Whitbeck, Walls, and Welch (2012), we believe that "Western" prevention and treatment scientists are largely unaware of the prevention and treatment work going on in AI/AN communities, and we urge a paradigm shift from adapting Western prevention and treatment science EBPs to creating cultural "best practices" from within AI/AN communities, incorporating relevant scientifically tested knowledge, and proceeding to evaluate the results. That paradigm shift is facilitated by understanding the differing epistemologies of Western, scientific, and traditional Native American approaches to healing.

Developing and disseminating evidence-informed culture-based interventions in AI/AN communities (as in all societies) involves shared cultural assumptions and values. As in all communities, practices and programs that work effectively are tailored to unique local contexts. AI/AN community contexts include tribal and class diversity, sovereignty, historical and continuing grievances, communication patterns, and economic marginalization. While context and culture, per se, are important to effectiveness, North American Natives are also the indigenous people of North American and, unlike other numerically minority peoples, AI/AN tribes have unique status and rights; this further increases the importance of local context and culture. The law requires respect and accommodation. The purpose of this chapter is to provide some guidance on the nature, role, and importance of culture and local context to those pursuing improvement in AI/AN services at the practice, program management, and governance levels.

Three major sources of evidence for knowledge informing behavioral health services are science, practice, and culture. *Epistemology* is the branch of philosophy that examines "ways of knowing" and, especially, how "evidence" works to yield both the content and certainty of a body of knowledge. Within that body of knowledge are "best practices"—that is, what a well-educated and experienced member of the culture would regard as the preferable way of doing things. A full-scale discussion of these epistemologies would be helpful but is beyond the scope of this chapter. The summary presented below is vital for those seeking to establish practices that are supportable in an indigenous world (as we have discovered, bridging the three worlds in our work). In our professional training and public education program, our mantra is *Science + Practice + Indigenous Culture = Best Practices.*

SCIENCE-BASED KNOWLEDGE

It is important for us to see science-based evidence, knowledge, and practice in a multicultural perspective. In particular, while valuing science we must avoid scientism, a belief that science is the only true way to acquire knowledge about reality and the nature of things; near-deification of the "scientific method;" flaunting the trappings of science; and preoccupation with "demarcation" between science and other ways of knowing. Science is, indeed, a powerful way of knowing, and the dependable scientific knowledge base has grown enormously. However, scientific information is far from perfectly true or dependable on its own terms (Ioannidis, 2005), and it is also constantly churning (Arbesman, 2012). The philosophy of science (including a dedicated association and journal) addresses epistemological and other issues in what we think of as the culture of science.

Science-based knowledge has driven technological advances, including agriculture capable of feeding a population plus generating surplus food capable of supporting specialists; manufacturing of tools and equipment; and healing materials and procedures, all resulting in Western prosperity and power (Diamond, 1999). Because of the tremendous success of basic natural science and science-based technology in botany/agriculture, physics/manufacturing, microbiology/surgery, and medicine, there has been a mistaken presumption of similar power in the area of

behavioral and social practice. But, especially in the social sciences, scientists and philosophers of science have adopted causal complexity, social influences, and pragmatism as the operative framework for scientific knowledge and practice, which places some philosophic limits on science-based knowledge in the social and behavioral health realms.

Contextual mediator and moderator variables (Baron & Kenny, 1986) change outcomes—for example, rural/remote versus urban setting contexts. There are other limitations on classical science in behavioral health. The appropriate scientific method depends on the characteristics of the research topic; randomized controlled trials are rarely appropriate for nondrug behavioral health studies. Human subject issues raised by the Belmont Report, the Helsinki Accord, the Code of Federal Regulations, and so forth constrain research designs; for example, a no-treatment control is prohibited while best extant treatment is required as the control; randomized assignment is difficult; and randomized selection is nearly impossible. Internal validity depends on sensitive research design, control, and measurement of all theoretically important variables (Lipsey, 1990). Further, the "unknown unknowns" among independent, mediator, and moderator factors can attenuate internal validity. Local and cultural context constrains external validity (generalizability). Where local context and culture are very strong factors (washing out the controlled variables), we have, de facto, evidence-informed community- and culture-based best practices.[8]

Behavioral medicine is greatly concerned with body–mind continuity and the meaning of illness and intervention. Management of placebo effects by bedside manner, reassurances, and similar practices are instrumental to outcomes. Not very amenable to control are

- *Choice*, a powerful factor in making an intervention work, which limits the scientific utility of random assignment
- *Self-healing belief*, guided by *expert healers*, which limits the scientific utility of blinding and double-blinding
- Guided development of *unique interpersonal relationships*, a key to health and thriving, which limits the scientific utility of controlling treatment conditions
- *Complex webs of interrelated and reciprocal factors* not reducible to simple, linear causal models, which limits the opportunity to isolate "active ingredients"

We mention some of the philosophic and logistic limitations on science-based knowledge in social and behavioral health science in order to leave room for the legitimate contributions of practice and, especially, culture-based knowledge. But scientifically developed information remains critical to quality improvement. Descriptions of interventions that are amenable to scientific study (i.e., specific, operationalized, and logically arrayed) are a concrete scientific advance over nonspecific, metaphorical description more typical of traditional knowledge. This entrée leads to other advances, especially evaluation of effectiveness by research methods that work in the local and cultural context.[9]

PRACTICE-BASED KNOWLEDGE

The utility of practice-based knowledge and evidence is acknowledged in the U.S. federal initiative *Service to Science*, as well as in the SAMHSA publication on multiple streams of evidence (Center for Substance Abuse Treatment, 2006), the Institute of Medicine report on the learning community (Institute of Medicine, 2005), and professional association publications (e.g., American Psychological Association, 2005).

Although practice-based evidence does perpetuate some ineffective or harmful traditions despite contrary scientific evidence, there is, nevertheless, rigor in its generation. Beliefs, principles, and theories acquired in training lead to in situ trial and error, which leads to methodical observation, which leads to professional opinion (American Psychiatric Association, 2011; Rust & Cooper, 2007). An intriguing recent example is the theory and treatment of phantom limb pain using mirrors and the hypothetical mirror neuron (Ramachandran & Hirstein, 1998). Practice experience is transformed into practice-based evidence by a rigorously structured process. Experts are assembled in conferences, work groups, Institute of Medicine roundtables, and similar venues. Published research evidence is presented to such expert assemblies. Practice experiences of participants and their colleagues are compiled and presented. The quality and meaning of data are debated by the expert assembly. Conclusions are drawn from evidence and a formal consensus process produces a document of guidelines or other

recommendations or standards for practice. The consensus (i.e., practice-based knowledge) is then disseminated in a structured manner. Practice guidelines are promulgated by professional associations. Program standards are adopted and applied by accreditation and standards organizations. Resource materials are distributed.

Practice-based evidence underlies the main body of knowledge available to, and applied by, all professional health workers, including Indian health workers working in AI/AN communities (Gray, Carter, Carter, LaFromboise, & Bigfoot, 2012). Advanced and continuing education and mentoring (Walker, n.d.) are the principal means of informing practice in AI/AN communities with both science- and practice-based knowledge and skills. Increasing the behavioral health workforce with practitioners who are educated, trained, and mentored in practice-based knowledge is by far the largest and most powerful entrée of evidence-based best practices into AI/AN communities' behavioral health services.

INDIGENOUS CULTURAL KNOWLEDGE, EVIDENCE, AND PRACTICE

We must have some knowledge of, and appreciation for, culture-based knowledge, evidence, and practice if we are to effectively participate in behavioral health services and to ameliorate disproportionate levels of behavioral health problems in AI/AN communities. Culture-based knowledge and evidence facilitates the derivation of new and improved culture-based interventions. Systematically documented, culture-based knowledge and interventions can lead to the design and application of culturally appropriate tests of efficacy/effectiveness, as well as a growing body of operationalized, sharable culture-based knowledge. Newly proposed culture-based interventions can be validated using evaluations consistent with AI/AN communities' assumptions, values, and epistemology (Cauldwell et al., 2005; Simonds & Christopher, 2013). Cross-walks among practice-, science-, and culture-based practices and programs can be identified. Culture-based interventions and the associated body of knowledge can be more efficiently and effectively disseminated throughout AI/AN communities to improve programs. Finally, the recognition and application of culture-based knowledge is an act of empowerment; this further strengthens AI/AN communities in their efforts to improve the quality of life of American Indians. Conscientious attention to culture-based interventions helps offset "historical trauma" and the inevitable culture, societal, infrastructure, and environmental wrecking that has accompanied conquest.

Culture-based knowledge deals with all the circumstances, survival challenges, and means of thriving and prospering that indigenous peoples have experienced over the millennia (Diamond, 2012) and the challenges they now face as a conquered, stigmatized, and oppressed minority population. Culture-based knowledge includes an extensive, practical knowledge of natural resources, such as agricultural, technical, and ecological uses; cultigens; medicines; and uses of flora and fauna. Culture-based knowledge of family and social milieu has been similarly critical to survival of the species. A body of spiritual beliefs has been developed by every culture to assist in coping with existence. Finally, culture-based practices have been developed over the millennia using trial and error to improve healing, health, and thriving. All human societies have developed and depended on traditional cultural knowledge for survival and thriving for tens of thousands of years before the Scientific Revolution—culture-based knowledge is effective to an appreciable degree, prima facie. While science-based knowledge and practice has hugely advanced healing, traditional culture-based knowledge and practice remain uniquely relevant and useful.

"Indigenous" refers to the first people to inhabit an area; it also means a prestate level of political organization—that is, chiefdoms, tribes, bands, clans, and family (Diamond, 2012; World Health Organization, 2013). Native North Americans lived mainly in chiefdoms. Indigenous culture-based knowledge and practice is characteristically tied to particulars—for example, the actual land on which indigenous people have been living; the web of relationships within a specific social context; and local linguistic expression, content, and meaning. Although the knowledge deals with particulars within a specific context, it also provides a connection through particulars to creation, all of nature, and the cosmos. It is a way of "grounding" a people's experience of existence. Equipped with this culture-based knowledge, individual traditional people have a sense

of relationship, a resource for taking responsibility for their own lives, and models of competent and correct behavior. These grounding anchors are central to behavioral health.

A traditional culture provides health definitions, beliefs about causes and treatments, historically proven (or, at least, accepted) health practices, and cultural assumptions and values not only underlying healing but also giving health itself a place among other concerns. The culture contains concepts of the causes of disease/disorder/injury, including spirits, gods, offenses, moral hazard, and random distribution. It has a concept of its own power/powerlessness, usually shaped by its experiences of conquest, catastrophe, plague, and so forth. Each culture has practices that exploit the power of the mind (e.g., the placebo effect) and social relationships and interaction (e.g., support groups, ritual, and ceremony) to affect health. Each culture has knowledge of substances (e.g., herbs), and the power of asylum and rest to affect health. Altogether, culture-based knowledge provides a substantial basis for effective healing, even in the context of today's science-based medicine.

NATIVE AMERICAN TARGET POPULATION

To understand culture-based knowledge and practice, we should know something about the target population. "Native North American" can be defined as people living north of Mexico since before the European invasion beginning in 1492. The size of the population at that time is undetermined and highly controversial, but subsequent mortality due to introduced infectious disease was of epidemic proportions, which remains salient today. There are now about 1.4 million Aboriginal Canadians (First Nations, Metis, Inuit, and others) (4.3% of the Canadian population) (Statistics Canada, 2011) and about 600 bands and reserves. About half the Canadian Aboriginal population lives on reserves. There are about 5.2 million American Indians and Alaska Natives (1.7% of the U.S. population), about half in combination with other races (Norris, Vines, & Hoeffel, 2012), close to 600 federally recognized tribes, and about 300 reservations. In addition, there are some state-recognized tribes, as well as tribes seeking recognition. There are approximately 300 spoken (or formerly spoken) indigenous languages north of Mexico, 269 of which are grouped into about 30 families.

The Native American group (like other aboriginal populations around the world) includes cultural subgroups that are very important for healing knowledge and practice. Traditional people who speak the tribal language and hold traditional beliefs are characteristically older, rural, and remote (although some younger, urban, and middle-class people are enthusiastically participating in a renaissance of traditional cultures). Reaching older, rural, and remote traditional people requires profound sensitivity to and understanding of culture-based knowledge and practice. Reaching younger people often requires a basic understanding of and manifest respect for culture-based knowledge and practice. Professionally grounded and trained people are serving reservation and urban Indian peoples and contribute a practice-based and bicultural perspective. They provide cultural guidance to Western professionals, when the latter are receptive. There are also established urban peoples who maintain a tribal identity as well as those who maintain a primarily Western identity. Some persons of Native American ancestry do not have a strong cultural identity, but most Native Americans have a healthy respect and affection for their cultural "roots," with or without cultural participation, contact, or knowledge.

Epidemiology and Etiology in AI/AN Communities

There is a large literature on behavioral health problems and their causes in AI/AN communities (e.g., American Psychiatric Association Office of Minority and National Affairs, 2010; Brodeur, 2001; Hendrix, n.d.; James, Schwartz, & Berndt, 2009; Jones, 2006; U.S. National Library of Medicine, 2013; University of Maryland, 2003).

An overview is presented in *Healthy People 2010* (U.S. Surgeon General, U.S. Department of Health and Human Services, 2000, and U.S. Department of Health and Human Services., 2001), which reports health-related data from the National Vital Statistics System, Centers for Disease Control and Prevention, and National Center for Health Statistics. In these documents, age-standardized rates of AI/AN suicide and homicide (all ages) are compared with total population rates. Death from all causes among older AI/AN youth (i.e., young

adults) is about 50% higher. Suicide rates are slightly higher, while homicide rates are, again, about 50% higher. Nonfatal physical assault is related to the prevalence of homicide and is about three times higher than the rate of the total AI/AN and non-AI/AN population. At the same time, unintentional deaths in total and deaths due to motor vehicle crashes, residential fires, and drowning are nearly double the total population rate.

Death due to cirrhosis of the liver (usually caused by excess alcohol consumption) is about two and a half times the total population rate, while alcohol- and drug-related crashes are triple. Adolescent alcohol use, accidents, and assaults seem to be the outstanding pattern; ameliorating these is a long-term goal of behavioral health treatment and prevention in AI/AN communities.

A follow-up report from the Centers for Disease Control shows progress toward reducing these target problems circa 2007 (Garcia, Kepple, & Hallquist, n.d.). Generally, there was some movement toward some health goals, but the disparities continue unchanged.

While epidemiologic data (especially statistics generated in the course of delivering public services) suffer from a number of errors[10] that affect comparisons between a subgroup and the total population, these epidemiological data still reflect a substantial opportunity[11] for improving the quality of life through behavioral health interventions.

Social Factors in American Indian/Alaska Native Communities

Epidemiology and etiology include the role of social factors in health status (Fig. 2.1). Social factors are a very large factor in health status (Geiger, 2006; Marmour, 2004; U.S. Surgeon General, 2012), particularly in AI/AN communities (Mikkonen & Raphael, 2010).

To improve health status, we must treat social factors rather than just the individual in clinical isolation. A substantial proportion of health disparities disadvantaging Native American peoples are attributable to the social factors of damaged cultures, environmental degradation, trauma of conquest and subsequent oppression, economic marginalization, and current low socioeconomic status.

Treating social factors includes dealing with the patient's circumstances but also directly acting upon the community and the culture. Thus, "culture *is* prevention and treatment" has action implications.

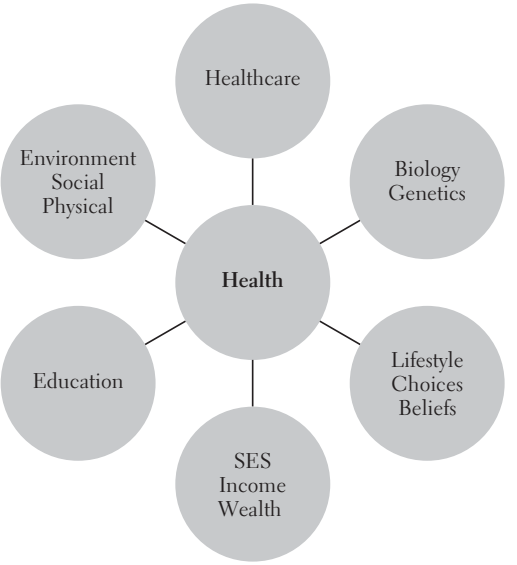

FIGURE 2.1 Major Determinants of Health Status

A LOGIC MODEL FOR CULTURE-BASED INTERVENTIONS

Participation in AI/AN communities to help ameliorate behavioral health problems and disparities is an art. One of the modes of entry into AI/AN communities for the One Sky Center has been helping tribes to construct logic models for federally funded projects. We successfully used Figure 2.2 in three national, multisite, multiprogram projects. We use this model here to frame a survey of some AI/AN communities' behavioral health service strategies. This survey provides a programmatic context for the reader.

The logic model guides description of a project by specifying what kind of descriptive content should be used and how it should be organized. It identifies key functional relationships to be explained (e.g., logical relationship among causes of the problem, interventions, and outcomes). Logic models are vital for grant writing, as well as planning, project management, and program evaluation. When a group of people builds a logic model together, the logic model also catalyzes the group process by providing a structure for bringing together diverse facts and perspectives.

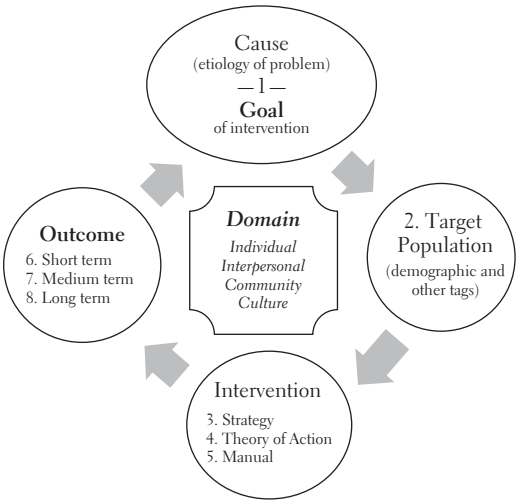

FIGURE 2.2 Logic Model for Behavioral Health Interventions

Logic models, too, are powerful communication devices, helping to bridge the gap between culture-based and evidence-based interventions. A culture-based intervention may initially be described as intervening in "a good way" according to an Elder's knowledge of tradition (An elder for the tribe, 2008), together with his or her wisdom and experience. While paying respectful attention is culturally appropriate and productive, translation into a scientific framework can also be feasible and useful. While premises of the culture-based intervention may include references to the spiritual, we can also find expression in analogous natural facts and principles. Behind traditional ways of doing things, there are often concrete facts and reasoned inferences. Beliefs, rituals, and artifacts can be treated both reverentially and as subjective phenomena described objectively. This bridgework is helpful for collaboration.

The logic model introduces a conceptual approach and a knowledge base more familiar to a science-oriented community. Logical description is an important mode of reasoning in a science-oriented community. Using a logic model facilitates theoretical and logical scrutiny, which strengthens credibility. The logic model lends itself to research design and measurement, which renders the intervention more amenable to independent evaluation and replication. That, too, strengthens the credibility of the intervention.

The logic model also has local utility, especially when drawn in a cultural format such as a medicine wheel or hoop. It stimulates a critical, rigorous review of an intervention by the culture-based intervention participants, which is helpful even when underlying belief in the intervention rests on tradition. Reconsidering presumptions about cause leads us to look for additional information and to redesign the approach accordingly.

Manualizing the intervention may lead to better scaling of the effort and allocation of resources. A manual also makes it easier to train and manage project personnel. In addition, mapping the chain of short/medium/long-term outcomes may lead to a more realistic focus. Altogether, the rationale for a logic model for a culture-based intervention includes its utility for the assessment, planning, and management of an intervention.

One Sky Center helped to develop a form to capture content for a program logic model, including definitions and examples, that was adopted by the Oregon Tribal Best Practices panel (Oregon Addictions and Mental Health Services, n.d.). This document is an example of both substantive and procedural collaboration with Native communities.

CULTURE-BASED PROGRAMMATIC STRATEGIES

Next we describe some culture-based programmatic strategies (item 3 in Fig. 2.2) that are in use in AI/AN communities today. Here we group programmatic strategies by domains of the target population (item 2, Fig. 2.2). These are strategies focused on individuals, families, public health, and culture itself. An illustrative overview, rather than an exhaustive research review, is our purpose here. We start with the individual domain.

Treatment of Individuals

The Matrix Model program (Matrix Institute on Addictions, n.d.; Obert et al., 2000; Rawson et al., 1995) incorporates a number of interventions into a comprehensive, intensive outpatient treatment program that has been successfully used in AI/AN communities. The Matrix Model is listed on NREPP (SAMHSA, n.d.a) as an EBP based on three experimental studies at a type 2 level.

Motivational Interviewing (SAMHSA, n.d.b) is a cultural adaptation of the established protocol (Miller & Rollnick, 2002), which is itself a further development of the Stages of Change model (Prochaska, Norcross, & DiClemente, 1994). Readiness to change and interventions that facilitate such readiness have long been known to be critical to the improvement of health. Motivational interviewing is listed on NREPP as an EBP based on six experimental studies at a type 1 level. Manual downloads for Motivational Interviewing/Enhancement in AI/AN communities are available at the One Sky Center site (Tomlin, Walker, Grover, Arquette, & Stewart, n.d.) and elsewhere (Venner, Feldstein, & Tafoya, 2006).

Intervention Focused on the Family

Some causes of mental illness, suicide, violence, and substance abuse lie within families. Families are also the victims of mental illness, suicide, violence, and substance abuse. Parenting is extremely important to the healthy functioning and development of a child (Kumpfer, 1999). Culture provides guidance and parents provide models together with close monitoring and discipline. When either is lacking or distorted, unhealthy behavior patterns may be transmitted and unhealthy behavior may be instigated. For example, parental neglect and abuse is a risk factor for a child's mental illness, suicide, violence, and substance abuse. Even average parenting skills may be insufficient to protect the child against toxic environments outside the family—for example, bullying at school or peer norms of risky behavior. Challenging child behavior can also overwhelm a parent's capacity to respond in a positive, constructive manner. Parent skill training can put the parents back in charge and help reduce the risk for mental illness, suicide, violence, and substance abuse and can improve health and thriving (Besaw, Kalt, Wilson, & Zemler, 2004; Kumpfer & Tait, 2002; National Indian Child Welfare Association [NICWA], n.d.).

The model program, Multi-Systemic Family Therapy, based on social-ecological and social learning systems theories, is one of the best-known parental skills interventions used in AI/AN communities (Littell, Campbell, Green, & Toews, 2005; Multisystemic therapy: Treatment model, n.d.). The original goal of Multi-Systemic Family Therapy was to improve the behavior of offending youth. However, the intervention deals with the broad spectrum of unhealthy behaviors, including those increasing the risk of mental illness, suicide, violence, and substance abuse. Interventions typically aim to improve caregiver discipline practices, enhance family affective relations, decrease youth association with deviant peers, increase youth association with prosocial peers, improve youth school or vocational performance, engage youth in prosocial recreational outlets, and develop an indigenous support network of extended family, neighbors, and friends to help caregivers achieve and maintain such changes. Specific treatment techniques used to facilitate these gains are integrated from those therapies that have the most empirical support, including cognitive-behavioral, behavioral, and the pragmatic family therapies. Other therapies falling into this model are Multi-Family Psychoeducational Psychotherapy (MF-PEP) level 4 based on four experimental studies, Multidimensional Treatment Foster Care (MTFC) level 2 based on three experimental studies, Multisystemic Therapy (MST) for Juvenile Offenders level 4 based on six experimental studies, Multisystemic Therapy for Youth With Problem Sexual Behaviors (MST-PSB) level 4 based on two experimental studies, and Multisystemic Therapy With Psychiatric Supports (MST-Psychiatric) level 4 based on two experimental studies (SAMHSA, n.d.c).

The American Indian Strengthening Families Program is an evidence-based family skills training program housed at the University of Utah and listed as a model program by SAMHSA under NREPP (Kumpfer, 1999; SAMHSA, n.d.d). Skills are taught in child, parent, and family sessions.

Home visiting programs are concerned with parenting. Early Childhood Home Visitation mitigates maltreatment, abuse, and neglect in order to prevent the development of illness, suicide, violence, and substance abuse later on. A thoroughgoing survey and evaluation provides an illuminating overview of programming and research in one area of behavioral health services in Native communities (Del Grosso, Kleinman, Esposito, Martin, & Paulsell, 2012). These authors were able to discover 19 programs and evaluated the quality of evidence as low ($n = 13$), medium ($n = 4$), or high ($n = 2$). They were unable to establish the effectiveness of these programs based on that evidence but did identify some lessons about EBP in tribal communities: the importance of tribal leader and community input into the adaptation of EBP, the

importance of cultural sensitivity and competence of staff, and the importance of building programs on cultural strengths and customs of the community.

Public Health Intervention Strategies

Continuing with the logic model, public health strategies bridge between strategies focused on the individual/interpersonal domains, on the one hand, and strategies focused on the community/cultural domains, on the other. Public health strategies are more influenced by the disease model of Western medicine than are the community/cultural domains, which we return to in the next section. The public health strategies focus on changing the immediate external causes, mediators, and moderators of mental illness, suicide, violence, and substance abuse in AI/AN communities. Public health strategies embrace and incorporate culture-based practices such as Gathering of Native Americans (Neumann, n.d.), adaptations such as "block parties" (Walker, Bigelow, LePak, & Singer, 2011, p. 328), as well as culture-based practices like powwow.

Risk Factor Reduction

A central public health approach is reducing exposure to risks. This can be achieved by removing the risk (e.g., closing down drug houses), by shielding the people at risk from the source of risk (e.g., establishing, monitoring, and enforcing rules), and by warning the people at risk about the risk (e.g., public education).

Many risk-reduction interventions for behavioral health problems are based on the theory that individuals make decisions based on information. Preventing unhealthy diet and lifestyle, substance abuse, risky sexual behavior, dangerous driving, suicidal impulse, bullying, violence, and so forth includes providing information on the consequences of risky behavior and methods of dealing with that risk.

One means of reducing exposure to risks is public education (also known as social marketing). Such campaigns use media, posters, lectures, and promotional events to raise awareness of risk, encourage risk avoidance in the general public, and mobilize the community's front-line institutions (schools, churches, workplaces, law enforcement, justice, and corrections) to eliminate risks. This public education approach is well known in its use to promote better diet and exercise and to discourage tobacco and excessive alcohol use. Participation of the Native community itself in developing and implementing the campaign is an important outcome.

Protective/Resiliency Factor Enhancement

Another central public health approach is strengthening resiliency and establishing protective factors in the community. The enhancement of protective/resiliency factors is one of the most frequently used approaches to mental illness, suicide, violence, and substance abuse prevention. Elders pass on culture via modeling, stories, advice, values, rules/guidelines for living, and a personal connection with the past. Hall and Raudenbush (2005) developed a protocol for this intervention called "Wisdom Teachings: Lessons Learned from Gathering of Elders." One Sky Center seized the opportunity to facilitate publication, distribution, and promotion of this document, which is an example of productive collaboration with Native communities.

The National Football League Players Association and Johns Hopkins Center for American Indian Health hold an annual Native Vision Sports and Life Skills Camp. AI/AN youth are taught sports by the professionals and engage in festivities. The messages to youth are stories of personal hardship, courage, and victory. Native leaders participate to encourage citizenship, respect for elders, and Indian pride. The Career and Life Skills Curriculum of the Native American Achievement Program at Arizona State University encourages achievement of academic goals, determination of career goals, attainment of leadership skills, and development of personal life skills. The outcome is persistence and graduation (Hammond, 2003), which has long-term health outcomes.

Techniques for resisting peer influence and asserting healthy self-interest are taught by NREPP-listed programs such as Promoting Alternative Thinking Strategies, I Can Problem Solve, Al's Pals, Improving Social Awareness-Social Problem Solving, Peer Coping Skills Training, Social-Moral Reasoning Development Program, and Viewpoints.

Natural experiment and case study methods have provided scientific evidence to prove the safety and effectiveness of a number of culture-based interventions, resulting in NREPP recognition for some,

including Project Venture (Carter, Straits, & Hall, 2007), a service learning program. Instructions for obtaining the program replication guide are available at the Project Venture site (Native Indian Youth Leadership Program, 2008). The service learning theory of action upon which Project Venture is based is that giving to the community (i.e., service) develops moral character, constructive habits, and a lasting emotional attachment to the community. In addition to the bonding aspects of service learning, these projects provide activity, challenge, and skill development.

The Zuni/American Indian Life Skills Development Curriculum is a school-based, culturally tailored, suicide prevention curriculum (LaFromboise, 1995; SAMHSA, n.d.f). It is listed as a model program based on two quasiexperimental studies with a quality of evidence that would be rated at level 2 or 3. This EBP teaches communication, problem solving, management of stress and depression, anger regulation, and goal-setting skills. It also increases knowledge of suicide. Methods are informing, demonstrating skill, and feedback on student performance. Outcomes are reduced suicide probability and hopelessness and increased problem-solving and suicide intervention skills. A manual is available (LaFramboise, 1996).

The Journeys of the Circle project, Canoe Journey, a Metaphor for Life's Journey program (Marlatt, Larimer, Hawkins, & et al, 2003), is a particularly good example of how scientific and traditional, culture-based approaches were combined to create an EBP (Marlatt, Larimer, Hawkins, et al., 2003). This program was developed over three years as part of the Journeys of the Circle Project, with the scientific and practice partner being the Addictive Behaviors Research Center of the University of Washington (Alan Marlatt, principal investigator) and the culture partner being the Seattle Indian Health Board (SIHB), a nonprofit organization serving the health needs of the Native community in King County, Washington, for more than 30 years (Ralph Forquera, director).

The program addressed culturally specific risk factors identified in the research literature: ethnic dislocation, acculturation stress, alienation from the larger culture, and unstructured time on reservations, during which drinking is also a response to boredom. The intervention strategy was to reestablish the canoe tradition; strengthen native identity; involve members of the community, canoe clubs, and canoe families; and build in the feature that all canoes are drug- and alcohol-free.

A comprehensive life skills curriculum was developed to help youth make choices that motivate positive actions while avoiding the hazards of alcohol, tobacco, and other drugs. It used a combination of life skills, activity, and community involvement. The eight-week skills course taught communication, decision making, goals setting, and other skills through the following eight sessions: The Medicine Wheel/Canoe Journey as a Metaphor; Who Am I? Beginning at the Center; Community Help and Support: Help on the Journey; The Quest: Goal Setting; Overcoming Obstacles: Solving Problems; Effective Communication: Listening to Others and Moods and Coping with Negative Emotions; and Strengthening our Body and Spirit.

A sample population (n = 50) was recruited from Seattle public school enrollments and outpatient service contacts at SIHB. The majority of participants were Native adolescents living in an urban setting. Assessment measures were the Comprehensive Adolescent Severity Index, past month substance use (tobacco, alcohol, marijuana, any drugs excluding tobacco), Rutgers Alcohol Problem Index, alcohol-related consequences, Situational Confidence Questionnaire, and confidence to resist the urge to drink heavily.

The research was of a one-group pre–post design. Results were trends toward reduced alcohol, marijuana, and other drug use and increased confidence to resist the urge to drink in multiple contexts. Participants reported a significant decrease in alcohol-related consequences at follow-up. The Canoe Journey evaluation may be classified as type 2.

A manual is available (La Marr & Marlatt, 2007). The Canoe Journey has now become a major event in the Pacific Northwest and Canada. One Sky Center again funded development of a Native community's local Canoe Journey manual for schoolchildren—another example of collaboration.

Intervention Strategies Focused on Community Competency

Community structure and functioning are sources of health and thriving of individuals (and families); in contrast, structural defects and dysfunction in

communities contribute powerfully to mental illness, suicide, violence, and substance abuse. Communities have, to varying degrees, the leadership, organization, and capacity (i.e., the community competence) to improve the quality of life for members, to provide opportunities, and to rise to challenges.

Unique opportunities also exist in indigenous communities for community mobilization. Resources for this mobilization include traditional values and principles supportive of healthy living and cultural content that can be applied to community mobilization.

Prochaska and DiClemente's (Prochaska, Norcross, & DiClemente, 1994) individual change model is the basis for quite a few community mobilization protocols, including the Tri-ethnic Center for Prevention at Colorado State University (2011). The Community Readiness Model is theory- and evidence-based, manualized, and supported with an extensive training program, together with quantified, normed community assessment.

The Community Readiness Model applies Prochaska and DiClemente's model of personal readiness for change to the community. The model not only assesses readiness for prevention interventions but also participates in mobilizing and moving an AI/AN community forward along the readiness path, instituting prevention as it progresses. The manual is downloadable. The One Sky Center developed a format for the next step after readiness, collecting community-wide data for a community to tackle a suicide epidemic (One Sky Center, 2005).

Gathering of Native Americans (GONA)[12] (Kauffman & Associates, 1999; Neumann, n.d.) is a four-day gathering for Native Americans who want to become change agents, community developers, and leaders. The GONA is based on several ideas: Community healing is necessary for prevention; healthy traditions in the Native American community are key to effective prevention; the holistic approach to wellness is a traditional part of Native American belief systems; every community member is of value in empowering the community; and the GONA is a safe place for communities to share, heal, and plan for action.

GONA takes participants through four stages of development—belonging, mastery, interdependence, and generosity. The cultural ideas communicated are healthy traditions and community healing, holistic approach, historical trauma, people's contribution to leadership and healing within a community, support and empowerment for people, rituals and teachings, feelings and healings into action, and use of a safe place. The outcomes are enhanced motivation for community action and understanding of the opportunities.

White Bison has published a seven-step approach to community development (White Bison Inc., n.d.a) and provides training for coalition building (Using Clan Knowledge) (White Bison Inc., 2004) specific to AI/AN communities. The method includes community readiness assessment, GONA training, and an adapted Community Anti-Drug Coalitions of America approach to coalition building and operations. White Bison Inc. is an organizational base for the Wellbriety movement, which includes a number of culturally based programs, projects, teachings, and materials aimed at improving AI/AN health (White Bison Inc., n.d.b). These include the Sacred Hoop Journey; Coalition Building through Clan Knowledge; Families, Mothers, Fathers, Sons, and Daughters of Tradition; Fire-starters; Warrior Down; The Healing Forest; and The Medicine Wheel and the Twelve Steps. Printed, video, and in-person training are available for these interventions.

Participation and collaboration by Western-trained health professionals include technical assistance using science-based knowledge and skills for gathering, evaluating, and implementing those techniques.

Intervention Strategies Focused on Culture

Cultures, like communities, can be made less risky, healthier, and better able to cope with threats to health and thriving. As an object of an intervention itself, culture is rediscovered and reinvigorated. Traditional strengths are preserved while evolving toward meeting current conditions. Rediscovery and reinvigoration of AI/AN culture is central to many AI/AN agendas, including nation rebuilding (Harvard Project on American Indian Economic Development, 2007; Honoring Nations Board of Governors, 2014). This is frequently a primary objective of AI/AN communities and the people who lead and serve them, so it must be a major principle of a culture-based strategy for AI/AN communities.

Rediscovering and reestablishing language, arts, ceremonies and identity is part of preserving the strengths of cultures that have been damaged by conquest and other adversities. Reestablishment

of institutions and self-government (sovereignty) (Harvard University, 2010) are among the strategies designed to strengthen such cultures.

At the same time, envisioning the future and identifying current opportunities for improving health, social, and economic status are essential to the health and thriving of AI/AN communities. One very well-developed strategy for revitalizing an indigenous culture is the Access to Determinants of Health developed by Four Worlds Institute (n.d). This protocol is logically stated, methodologically thorough, and well documented.

The health and thriving of individuals (and families and communities) is supported and directed by a culture, but culture itself requires participation and nurturance from its people, as well as contributions to its constructive evolution. Badly damaged cultures are a major contributor to youth suicide, violence, substance abuse, and pathologies of all kinds. Maintenance of healthy culture, treatment of sick culture, and rehabilitation of badly damaged culture require civic leadership as well as popular participation. Important aspects of civic leadership include both "how to do it" (methods) and the "vision."

Culture *Is* Treatment and Prevention

The belief that "culture *is* treatment" has been advanced by professionals, government leaders, and AI/AN activists (Brady, 1995; Gone & Calf Looking, 2011; SAMHSA, n.d.g; White Bison Inc., n.d.d). Cultural teachings, practices, and social conventions yield balance of mind, body, spirit, and emotions. Living in a good way, as guided by cultural leaders and written in the heart, will bring behavioral health. Traditional cultural beliefs and practices constitute a principal form of treatment and prevention, per se. "Culture *is* prevention" means an awareness of (and participation in) the values, traditions, ceremonies, and sense of community, per se, that improves health and thriving while preventing mental illness, suicide, violence, and substance abuse (White Bison Inc., 2014).

Culture as an intervention shares the stage with Western-style risk-reduction and protective interventions for mental illness, suicide, violence, and substance abuse. As an intervention, culture (consisting of stories, ceremonies, knowledge, skills, values, and so forth) is used to strengthen individuals, families, and communities. As an intervention, culture provides constructive, time-filling activity as well as social services and productivity. As an intervention, cultural activities provide social contact and a vehicle for the communication of caring. A common culture-based intervention is reinstituting a traditional mentoring relationship between elders and youth.

There are many culture-based interventions, each to be found in different forms at different times and cultural locations. These are described in a great many documents, many of which are not part of any professional literature. Documentation and artifacts are being collected in university and government archives. We will mention several interventions that have some application in the prevention and treatment of mental illness, suicide, violence, and substance abuse as part of the global goals of culture-based interventions. General descriptions are provided, but there are tribal and community variations within each intervention.

Flute playing is used, like meditation, in self-discovery and self-healing. Dancing, fasting, drumming, making of relations, medicine wheel, naming, pipe, powwow, potlatch, giveaways, honoring, rites of passage, ritual art, masks, sand painting, shaking tent, singing, and smudging ceremonies are culture-based interventions to promote health and thriving, bring good fortune, and heal. These interventions produce trances and visions, focus and entrain the mind, and connect to the spirit world. They establish and strengthen interpersonal relationships; create or transform identity; provide instruction on values, morals, principles, and behavioral protocols; and relieve feelings of loss, guilt, and fear. They apply to mental illness, suicide, violence, and substance abuse in individual, interpersonal, and community domains. Recognition, respect, and referral are the collaborative entrées.

CULTURE-BASED TREATMENT TECHNIQUES AND TECHNOLOGIES

In this section, we describe culture-based intervention in its own terms, but with reference to Western analogues. We draw from literature on aboriginal peoples worldwide but focus on Native Americans, especially American Indians. This background is helpful for partnering and bridging between culture-based interventions and EBP.

Until 1,500 (ancient civilizations' medicine), 500 (beginnings of Western medicine), or even just over 100 years ago (beginnings of modern Western medicine), all humans relied entirely on culture-based, traditional healing to cope with disorders, diseases, and injury, as well as behavioral problems. Some still do. With 100 billion neurons, 100 trillion synapses, and a lot of observation, trial, and error over long periods of time, prescientific humans did a pretty good job of developing knowledge and practice to maintain their health status. There were some iatrogenic healing practices, but that is also true of modern medicine. Traditional healing could not ameliorate every illness, injury, or disorder, but neither can the best, modern, science-based medicine and surgery, let alone modern behavioral health services.

Worldwide, culture-based knowledge and interventions have some notable characteristics. They rest heavily on ideas about the spiritual world, its entities, and their connection with the "real" or waking world. They seek harmony as a primary condition leading to health. They use meditation, mindfulness, and other psychological techniques to access the powerful mind–body connection. They use magic (e.g., the illusion that a foreign object is being removed from the patient's body by a medicine person using a suction pipe). They also use herbal and similar remedies, many of which are found in refined forms in pharmacies today (e.g., willow bark/aspirin).

It is important to bore down below programmatic strategies for the fundamental cultural perspective on healing. One website gives a concise description of some healing practices (Dancing to Eagle Spirit Society, 2008b). Some of the features of American Indian traditional healing include a healer in costume, sucking out pathology with tube and hands, and then disposing of the pathology by burial; display and use of medicine bundles; communication with spirits via trances; performing curing songs, dances, drumming, spells, and feasts; conducting purification ceremonies; administering herbs (topical, fumigant, emetics); representing health-related forces by sand painting; playing of musical instruments to entrain mental process (e.g., eliciting theta waves); use of costume, fetishes, charms, animal and vegetable substances; propitiation of spirits; and involvement of family and community ("social support"). Healers develop competency through dreams, inheritance, apprenticeship, and the usual trial and error.

Notable characteristics of culture-based healing in AI/AN communities include storytelling, myths, sacred symbols and artifacts, ceremonies and rituals, shamans, medicine people, and traditional healers. Healers' recommendations to patients include lifestyle changes, offerings to spirits, diet, improved knowledge of language and culture, meditation, and engaging in certain treatments. The outcome of the diagnostic process is focus, expectations, commitment, and mobilization of effort.

This body of knowledge and practice is very complex and takes a great deal of training, practice, and experience. No unqualified person should aspire to deliver these services; . Serious Adverse Events are a real risk. It would also be seen by the target population as presumptuous, which undercuts the critically important trust of the community (Aldred, 2000). However, when practicing in AI/AN communities today, it is important to appreciate traditional healing and to be ready and able to collaborate with indigenous healers, as demonstrated by the Nuka system of care in south-central Alaska (Gottlieb, 2013).

American Indian Traditional Medicine

American Indian healing practices include (to put them in Western terms) teaching and learning, counseling and persuasion, shaping expectancies, social learning, use of placebos, mythology and storytelling to provide guidance, training in self-regulation, herbals, and food and fun. We can see some parallels and underlying commonality between Western and Native American approaches in the following details.

Culture-specific elements of mental health, suicide, violence, and substance abuse prevention (e.g., White Bison, Sons/Daughters of tradition [White Bison Inc., n.d.c]) aim to make members of the indigenous culture feel valued, included, empowered, and responsible—these are an offset to historical marginalization and oppression. Culture-specific elements tailor interventions by means of culturally appropriate language (e.g., passages of text, speech in indigenous words—which are powerful whether understood or not), terminology with special meaning (e.g., "all my relations"), traditional graphic elements (e.g., use of circles more often than lines, use of symbolic feathers), significant items of traditional dress (e.g., ornamentation), concept-laden symbols (e.g., medicine wheel), ceremonial music (e.g., drumming),

culturally specific forms of common social process (e.g., diplomatic protocols for expressing honoring and respectfulness), social institutions (e.g., powwow), references to social structure (e.g., importance of lineage, clan), ideas of spirituality and universal relatedness, and so forth.

Culture-specific aspects of mental health, suicide, violence, and substance abuse prevention respond to the culturally unique meanings of those disorders, identify and address the culturally unique risk and protective factors for those disorders, and identify and use or accommodate culturally unique interventions.

Adaptation of EBP interventions includes dealing with causes of mental health, suicide, violence, and substance abuse unique to the circumstances of many AI/AN communities, and taking advantage of treatment modes that are believed in by members of those communities. Adaptation is not a simple process (Castro, Barrera Jr, & Holleran Steiker, 2010). The EBP takes on unique traditional elements (BigFoot & Braden, 2007; BigFoot & Funderburk, n.d.; BigFoot & Schmidt, 2010). Healing from loss, recovering from trauma (directly experienced or historical), healing from sexual abuse, and transforming normalized co-dependent thinking processes are required for many members of AI/AN communities with behavioral health issues. The twelve-step process of Alcoholics Anonymous is a well-known protocol that is similar to a number of interventions for the target population of addicted persons (e.g., "The Red Road to Sobriety"; White Bison Inc., 2002). Discovering and rebuilding individuals' cultural identity through flute playing, working with horses (e.g., Native American Horse Program; Oregon Addictions and Mental Health Services, n.d.), traditional meditation, and mentorship by elders are unique opportunities that AI/AN cultures provide for individual treatment of at-risk persons. Others include storytelling, sweat lodge, and talking circle (Oregon Addictions and Mental Health Services, n.d.).

Integrated medicine: AI/AN culture and traditional medicine are also used as a partner with Western medicine and healing (e.g., the Nuka system of care in south-central Alaska; Gottlieb, 2013). It is used to create expectancy and engagement of patient, healer, family, and community. Some of the treatment is provided by traditional medicine people. Controlled research showed that spiritual healing sessions are effective in creating high expectations in both healer and patient (vs. controls) and, subsequently, greater improvement in objectively evaluated medical outcomes (Wirth, 1995).

Definitions: AI/AN healing includes beliefs, practices, botanical medicines, religion, spirituality, and rituals among the several hundred AI tribes and AN villages. AI/AN traditional healing and medicine means "practices shaped by long-standing cultural world-views and values" (Johnston, 2002). Etiological theory includes offending spirits, being victimized by witchcraft/spells, poisons, and living in disharmony. The healer is an intermediary between spirit and living worlds in the context of a living world infiltrated by a powerful spirit world (Moulton, 2001). It is concerned at least as much with prevention as curing. When curing has done all it can, traditional healing provides comfort, support, and reconciliation to the natural course of life, including morbidity and mortality. Religion and spiritual matters are completely intertwined with health. Principal goals are balance in the four realms of spiritual, emotional, mental and physical health; following a cultural path/routine; and sharing in the cycle of life (Hunter, Logan, Goulet, & Barton, 2006). Purification, cleansing, and cognitive change are central themes.

Spirituality of AI/AN people is crucial to their culture-based practices, as to everything in the traditional AI/AN way of life. Traditional belief is that everything has a spirit—celestial bodies, flora, fauna, inanimate objects (like bodies of water), and people. These spirits exist both in a spirit world and in the observable, material, waking world. Knowledge is received from the spiritual world, as are healing influences. A state of harmony with the spirits is sought—good health and thriving depend upon it. Connection to the spirit world is a sophisticated religious practice of healers, especially those known to the Western world as "shamans."

Goals of AI/AN traditional medicine and healing are wholeness, balance, harmony, beauty, meaning, spiritual well-being, restoration of emotional and physical health, and well-being (Cohen, 2003). Traditional healing and medicine confront imbalances, negative thinking, and unhealthy lifestyle. The outcome of such interventions is restoration of well-being and harmony and change of thought, feeling, and behavior. In particular, indigenous medicine has the task of healing emotional pain. If anything, AI/AN healing is more concerned with behavioral health than physical, although that distinction is not made. It focuses on psychological/spiritual healing of

the person (or community) even more than curing a disease.

Exposed to many traumas and much pain, and with little access to Western medicine, even for the illnesses, disorders, and injuries with which Western medicine does best, AI/AN peoples have had to rely on traditional healing and medicine by default. In dealing with disease, the goal may not be a cure. A good transition into the next world is important, even when mortality cannot be prevented.

"Health" means a person has a sense of purpose, follows inner guidance (inscribed by the Creator), walks on a path of beauty, lives in balance and harmony, has good thoughts, is grateful, and is respectful and generous (Cohen, 2003). One concept of illness is fragmentation of the soul, with some parts lost to another dimension or reality or world. This soul illness is very much a part of mental illness, suicide, violence, and substance abuse. The West knows this sort of condition as dissociation or, in other cases, depression with its sequelae (Kramer, 2005). The goal of soul healing is to attract back those lost soul fragments.

Because illness is a matter of morality, balance, and spiritual forces, not all presenting problems are treatable as health problems. Some are nature's retribution (for disrespect or violation of taboos). Some are an expression of self-centeredness, unbalanced living, or feeble constitution. These illnesses (or threat of them) serve a social purpose: protecting the integrity of the culture. Some illnesses are imposed by sorcerers or nonhuman evil entities. Some illnesses involve the intrusion of supernatural objects. Other illnesses initiate transformational passage to a higher level of being or a new role.

Diagnosis rests on experience and acute observation, while the more overt adjuncts to diagnostic procedures include communication with spirits, sacred bundles, pipes, masks, and so forth. Intuition, sensitivity, and spiritual awareness are key assets of traditional diagnosticians. The healer engages the patient by explaining his or her philosophy and plausible causes of illness and acceptance of offerings and gifts. Among the causes a diagnosis may reveal are discord in prominent social relationships (e.g., male/female; Quintero, 1995). Other causes are cruel words, abusive behavior, and violence. Failure to love and care for one's spouse and children, and desertion of them, are taboo violations causing illness in the person, community, and tribe.

Treatment includes teaching, mentoring, and counseling; ritual, ceremony, prayer, and songs; laying on of hands; smudging; community ceremonies (e.g., chanting, singing, dancing, and sweat lodge); and botanicals. Traditional practitioners use the most powerful intervention known to any healing practice: skillful and effective use of the well-known, powerful, but sometimes misunderstood "placebo" (mind–body) effect (Bonvillain, 1997).

Prayer helps to focus the mind on harmony and balance among all things, free of anger, fear, and strife. Music invokes ideas and its rhythm entrains the mind. Smudging affects consciousness, feeling, and sensitivity through the ritual, possibly potentiated by the aerosols. (The sense of smell remains the most evocative of our senses.) Oral and topical application of botanicals also involves rituals, an active ingredient in addition to the activity of the substance per se. Massage is used in a fashion more like acupuncture than sports medicine—it helps to visualize the disorder and the healing process.

Counseling may be potentiated by sacred venues like ceremonial lodges and associated sacred rituals. Ceremony affirms cultural values and identity and involves communicating with spirits, placating them, and gaining release from their perceived controlling influence. A sweat lodge ceremony can overcome avoidance and denial and get the patient back in touch with primal wisdom (i.e., doing what he or she already knows is right).

Mehl-Madrona (1999) identified eight principles of traditional healing: healing takes time and time is healing; healing takes place within the context of a relationship; achieving an energy of activation is necessary; systems are isomorphic (biological, psychological, cosmic); self-discovering in peace and quiet (avoidance of distraction); awareness of emotions; bed rest; and ceremony. Following are some examples of traditional treatments.

Medicine Wheel: The Medicine Wheel, also known as the Sacred Hoop (Laframboise & Sherbina, 2008; Montour, 2000) is a framework and symbol of healing as well as a grounding in the life cycle, range of personal characteristics, seasonal cycle, and geographic location. The four cardinal points (east, south, west, north, and sometimes up/down) are occupied by spirits. This is the design of the medicine wheel that is depicted and used throughout AI/AN communities (Cohen, 1998). Many ideas about existence, including the cycle of life, and many structures

and activities, including healing ones, are physically oriented to this design. This template is particularly useful in describing behavioral health programs in AI/AN communities.

Wiping of Tears: The Wiping Away of Tears is a traditional ceremony to purge survivors of resultant destructive emotions and thoughts. Sacred objects and materials are used and songs are sung. It includes forgiving those who caused pain and loss of life. Tears may be symbolically washed from the faces of victims and grieving mourners. The ceremony ends a period of mourning, leaving victims with reduced pain and allowing them to move on.

Sweat Lodge: A sweat lodge ceremony (Laframboise, 2008b; Windwalker, n.d.) is a widely used and flexible ceremony that involves steam generated by hot rocks in a dark enclosure. Water, sometimes including herbs, is applied to the hot rock by a medicine person who also leads the ceremony. The ceremony includes the medicine person, subject, relations, and guardians. The sweat lodge has spatial orientation (four directions, spirit world) and is constructed to hold in heat and be dark. There is an important etiquette. The ceremony is a tangible and decisive commitment to accomplishing something and requires fortitude. The outcome is physical and mental experiences (purification, renewal, and fresh start) and affirmation of an individual's sense of personal and cultural identity.

Talking Circle: The talking circle (Bureau of Indian Affairs, n.d.; Running Wolf & Rickard, 2003; Umbriet, 2003) is a group activity that enables orderly expression, unburdening, and consolation. The circle is a symbol of connectivity and completeness. The outcome is emotional and social healing. (Western group therapy and support groups operate in a similar way for similar purposes.)

Vision Quest: The vision quest (Bentley, n.d.) begins with a premise that individuals are put on the earth for a reason, but that reason is often unclear. Chandler and Lalonde (2008) have demonstrated the causal relationship between personal vision and suicide. The vision quest is a very serious, arduous journey into the spirit world to learn what that purpose is. It involves extensive preparation and guidance from a medicine man. Symbolic objects are made or gathered, prayers are said and a mindset is created, a ceremony is held, and the supplicant is taken to a certain spot where he remains for a given period of time, during which he prays and has visions. Then he is brought back to share the vision with the medicine man and to integrate the experience into his life. An important anthropological text, *Black Elk Speaks*, illustrates the acquisition of a vision and the lifelong process of spelling out its implications (Neihardt, 2008).

Many more traditional healing practices are listed by Echo-Hawk (2011) and Dancing to Eagle Spirit Society (2008b).

Theories of Action

We infer theories of action (item 6 in Fig. 2.2) underlying strategies. Following are some theories underlying the range of culture-based interventions. Some of these might be described as techniques, but they also get to the theories underlying culture-based techniques. Identifying, spelling out, and testing these theories is on the science agenda for culture-based knowledge.

Storytelling

There are two aspects of storytelling to understand: the content of the stories and the psychology of the *telling*. The content of stories relates personal experience to myths, provides moral instruction, transmits ethical values, and provides an education on the relationship to land and traditions. Many stories are now posted on the Internet (Native Daughters, n.d.). They need little or no interpretation. Dreams, too, are fragmentary stories. They are easily thought of as communications from the spirit world that can be decoded by wise elders, shamans, and psychoanalysts. Stories have characters, predicaments, and attempted extrication—a virtual reality for the critical themes of life. Stories facilitate practice in social skills and allow the freedom to experience scenarios without the full consequences. The content of stories is often cultural myths that contain shared beliefs and values. Thus, the content of stories and dream-stories provides a therapeutic tool for healers.

Telling stories involves powerfully healing and instructive psychology. The human mind has a drive to find meaning; it cannot accept uncertainty, randomness, and coincidence. Stories provide explanations for fragmentary and ambiguous information. This drive appears so powerful that certain neurological injuries compel the individual to invent implausible

stories to explain inconsistencies, to which the victim adheres tenaciously (Ramachandran, 2011; Sacks, 2012). People tell or hear stories 24/7, not passively but eagerly and actively (Gottschall, 2012; Simmons, 2001). A storyteller has ready access to the mind, and a skillful storyteller takes over the audience's mind with just a few words. Stories can move and change us; they have significant power over us. Stories activate sympathetic physical responses. When stories are told by grandmothers, medicine persons, and significant others (as opposed to simply reading them), they carry additional impact related to the storyteller and the setting (e.g., family living room, community lodge). Ritual, musical, and other adjuncts further add to their impact. Both the content and the telling of AI/AN stories are important for treatment purposes (e.g., Native American Story Telling; Oregon Addictions and Mental Health Services, n.d.).

Native American Myth

Like every society, including modern European and North American ones (Campbell & Moyers, 1988), Native Americans believe the natural world is paralleled by and interlaced with a supernatural one. There are differences in the exact nature and powers of the saints, deities, and spirits; the ways they are depicted and the protocols for addressing them; and the forms in which all of these concepts and practices are assembled into a "religion" with officers, edifices, and rituals. But all human societies have developed (or, as they may prefer to put it, have had revealed to them) spiritual concepts and practices to help explain and cope with existence.

Survival for hunter-gatherers and small-scale agricultural communities until very recently was more precarious than we can imagine. With a few exceptions, life was short, dangerous, brutal, and riddled with illness and starvation (Diamond, 2012). These societies had to develop an empirically based body of knowledge and skills in each major area of life (e.g., hunting, fishing, vegetable and fruit gathering, agriculture, war, and health maintenance). Where dependable, sufficient natural resources and peace prevailed, tribes were quite successful.

Native American spirit knowledge is conveyed in myth and legend by storytellers (elders), singing and drumming, and carvings and paintings. The nature of this body of knowledge and practice varies among tribes and over time, but there are fundamental themes.

One fundamental theme that bears directly on behavioral health is the way Native Americans see and value a bond with nature, animals, and the land. Among special relationships are animal protectors. The condition of these bonds and, in particular, harmony is central to health. Actual physical disruption of the relationships (ecological degradation, ceremonial lapse) is distressing and pathogenic. Health interventions are focused on improving these relationships for both individuals and communities.

Native American myths also include origin, creation, and creator tales. These are key assumptions in individual identity and all forms of group activity. Many motivational interventions use these concepts to drive behavioral healing. Meetings normally begin and end with appeals (prayers) built on these concepts as a means of orienting participants and encouraging dedicated effort. Even when secular professionals are leading meetings, it is proper protocol to request elders or other traditional individuals to speak the prayers, during which they sometimes convey keynotes for the meeting.

Myths are part of everyday life, explaining, inspiring awe, and identifying action implications, for example (American Folklore, 2013; Native Languages.org, n.d.; StoneE Producktions, 1996). A coyote crossing the road requires an appropriate response, as delineated in some tribal myths. Food is set aside for ancestor spirits, as stipulated in others. Every natural phenomenon has its spirit and is regarded accordingly in daily activity. Spiritual and supernatural stories about natural entities—geologic features, plants, animals—explain and remind people of their meaning and utility (where later Western society puts such entities into phylogenetic classification systems). These myths are often used in healing to explain what has happened to the patient and what to do about it. Myths cross-walk to Western diagnoses and therapy to some degree.

Myths explain the presence of resources such as food and the befalling of adversity such as bad weather, disease, and failure to prevail. Many myths identify taboos and their enforcement by supernatural powers. Spirits can be offended, alienated, and angered. The myths also indicate what remedial actions may be taken. Propitiation, obedience, and offerings are important instrumental behavior. Taboo violation is important in explaining behavioral health

problems and gives patients something to do about their remediation. Remedial action may be quite similar to many Western therapeutic recommendations.

Soul Flight, Retrieval

A number of cultures around the world have a notion that parts of the body, especially the soul, disappear, which underlies morbidity. Among Native American tribes there is a soul theory that includes the idea of soul flight. This is important for the explanation and treatment of mental illness. The patient may have been invaded by a bad spirit that carries off the soul, or the soul may have left as a result of conflict and trauma. The treatment is administered by a shaman who, as a result of a special relationship to the spirit world, finds and rescues the soul by means of a journey (Ingerman, 1991; Torres, 2002).

"Souls" are the source of life and vitality, emotions, feelings, and sentiments. Souls leave the body as a means of surviving intolerable experiences of accident, violence, abandonment, dishonor, and so forth. The patient experiences something like exacerbated major depression with deep apathy and/or severe anxiety. Even more common is a sense of incompleteness, disconnection, and dissociation. Consequences also include physical illness, addiction, and debilitation. The presenting signs and symptoms are well known to Westerners, but Native American etiology and treatments differ somewhat.

The shaman uses rattles, magic objects, soul catchers, and medicine bags to facilitate the session (analogous to medical paraphernalia). The patient is surrounded by family and community supporters (at the treatment event, not ancillary to it). Drumming affects the shaman's brain wave patterns, leading to a trance. The shaman passes into the spirit world and, with the assistance of a guardian animal and other helping spirits, tracks down the soul in a dreamlike world in which time, space, and other waking-world parameters do not apply. Strong intention (commitment) on the part of the patient and the shaman is required. In the course of the journey, the shaman develops an explanation for the soul loss. The shaman catches or persuades the soul to return to the waking world. The shaman reinstates the soul in the patient's physical body by blowing it into the heart and brain. Then the shaman recounts the journey, providing the patient with insight. The patient goes forward, integrating the contribution into his or her life.

A Western professional versed in phenomenology is able to accept this view of reality and the effectiveness of the practice and identify cross-walks and possible opportunities for collaborative treatment. With both patient and healer convinced of efficacy, soul rescue is similar to the role of Western "talk therapy," except that the shaman with his store of cultural knowledge (which the patient shares) is driving the insight. As in Western therapies, the work is not over when the session ends.

Shamans, Medicine People, Healers

The healing practice of the shamanic tradition is based on their special relationship with the spirit world, as well as charisma, dramatic talents, and insight skills. The premise is that compliance with rules and respect for spirits of nature and ancestors bring wellness and good fortune. Causes of illness include disobedience; lack of respect; projection of a foreign object into the victim's body by hostile spirits or sorcerers; and the victim's soul having been stolen, lured away, or left the body. Shamanic treatment includes extraction of foreign bodies, tracking and rescuing the soul, and calling upon the healing power of nature spirits. To apply this treatment, shamans make contact with spirit world during trance.

In addition to shamans, there are other kinds of healers in AI/AN communities, including medicine people, diviners, and herbalists. They contribute to healing by leading ceremonies, rites, songs, and dream interpretation. Some of the ceremonies include sun dance, vision quest, rites of purification (sweat lodge), funeral rites, and puberty rites. They employ physical tools such as costume, pipes, dream catchers (Laframboise, 2008a), and medicine bundles (Dancing to Eagle Spirit Society, 2008).

Over tens of thousands of years, a great deal of cognition has been applied to creating and evaluating cultural instrumentalities (e.g., the spirit and dream world; description and classification of the natural world with demons, monsters, guardians, heroes, and personages for animals and natural phenomena), to explaining significant objects and events through myth, and to enabling people to cope with existence through propitiation, remediation, healing, seeking guidance, protection, requesting supplies of natural

resources, as well as requesting relief of deprivation and duress.

Placebo: Relationship; Ceremony/Ritual; Meaning

While medicine and surgery are less developed in traditional healing, we are beginning to understand the very powerful placebo effect underlying some healing, techniques that effectively elicit the placebo effect for healing purposes, specific methods of placebo action, and the extent and limitations of its usefulness (Beecher, 1955; Kaptchuk, 1998; Kaptchuk, Petrovic, Wager, & Benedetti, 2013; Moerman, 2002). Placebo research yields complex facts, principles, and theory: Placebos are neither as miraculous as some enthusiasts believe nor as inefficacious as some critics assert. The placebo effect refers to use of the mind–body connection to produce health-related effects. The important "continuous subjective" outcomes are clearest (Harvard Medical School, 2012). The curious case of phantom limbs and the amelioration of associated pain cast some light on the underlying neurology of some placebo effects (Chan et al., 2007; Ramachandran, 2011; Ramachandran & Hirstein, 1998). Similarly, we are also beginning to understand the role of "harmony," "personal continuity" (Chandler & Lalonde, 2008), social status or social factors (Marmour, 2004), and relationships in health and healing. These factors are very culture-bound (at the phenotypic level), and clearly they all have some significant part to play in etiology and healing.

Herbals

In *Native American Medicinal Plants*, anthropologist Daniel E. Moerman (2002) describes the medicinal use of more than 2,700 plants by 218 Native American tribes, including 82 categories of medicinal uses, including analgesics, contraceptives, gastrointestinal aids, hypotensive medicines, sedatives, and toothache remedies. Some of these herbal treatments have been reviewed by the Mayo Clinic (2010) and the National Geographic Society (Johnson, Foster, Low Dog, & Kiefer, 2010). Many of the active ingredients are now provided in a refined form in drugstores with greater purity and consistency of dosage. Although herbals are chemical substances, the results of scientific studies of herbals are somewhat like those for placebos. Furthermore, their medicinal action is somewhat conflated with the placebo effect. While the "little white pills" generally come with dry pharmacologic fact sheets, herbals come with a body of aboriginal lore that can explain and potentiate the effect of the herb. Altogether, indigenous peoples had a pretty well-developed pharmacopeia.

Process of Teaching and Learning

Behavioral health prevention and treatment everywhere include guidance and information for living and healing ("counseling"). Learning and guidance in dealing with current conditions are transmitted through traditions, ceremonies, and daily observations. Self-knowledge and capabilities are realized by dealing with challenges and decisions based on learning by experience, observing, listening, and participating in cultural activities. In Western terms, learning includes shaping expectancies (Kirsch, 1999; Rotter, 1954) and social (observational) learning of behavior and consequences (Bandura, 1977).

Theories, philosophies, histories, ceremonies, and stories are ways of knowing about life and living, as are talking circles, participant observations, experiential learning, modeling, meditation, prayers, ceremonies, and storytelling. The cultural life of the community consists of many of these teaching events, some in response to special events, some as life-cycle passages, and some annual ceremonies. Observation and doing, authentic experiences, individualized instruction, and enjoyment inculcate proficiency as a member of the culture. Importantly, children participate even before they understand what is going on.

Members of the community are responsible for acquiring, possessing, and sharing/teaching knowledge, which results in oral and symbolic transmission from generation to generation by modeling, practice, and animation. The knowledge they pass on is embedded in songs, ceremonies, artwork, the language, worldview, and "teachings." Elders have a special responsibility, authority, and respect in regard to this task (Hall & Raudenbush, 2005).

Healing is accomplished by use of teaching and learning to anchor the individual in his or her culture and its resources. Some Western collaborative efforts, including those of One Sky Center, consist of building local cultural assets into evidence-based modules such as home visiting protocols (achieving school

readiness by telling traditional stories combined with learning to read them).

Fun and Food as Treatment

Many administrators and budget analysts cannot abide the thought of expenditures for fun and food as a line item in a program budget. Yet fun and food are powerful therapeutic tools. Both are attractive, which facilitates engagement; both catalyze interpersonal warmth and bonding; and both are positive reinforcements for desired behavior. Many preventive and treatment events in AI/AN communities depend upon fun and food. Feasting is essential to most Native American cultural events. The collaborating Westerner should help justify fun and food with Western behavioral and social theory, use budgeting creatively, and plan on using this potent intervention.

Bottom Line on Culture-Based Interventions

Again, the purpose of this section is to enable behavioral health providers to appreciate and collaborate with indigenous healing in AI/AN communities. Providing behavioral health services that work in AI/AN communities is no simple matter. Non-Indians have to abandon some Western baggage, embrace the assumptions and values of AI/AN communities, and develop an unusually deep understanding of what works and how. We have to see beyond the superficial face of what passes for efficacious in each culture to grasp the underlying "active ingredients." Some indigenous beliefs are fallacious and some practices are ineffective or even harmful, but the same is true for some Western beliefs and practices. "More research is needed," and, in the meantime, an open and flexible mind is imperative. Success in collaborating with Native communities depends on sensitive and thoughtful inclusion of culture-based interventions.

PROGRAMS, PRACTICES, AND KERNELS

Sources such as the NREPP describe complete packages of procedures and contexts, better known as "programs" or "model programs." Programs are packages of practices together with service delivery, and structural components, such as 28-day residential, nurse-family, multisystemic, assertive community therapy, and so forth. Programs have "core components" that are thought to be responsible for program outcomes. Replication of programs with the expectation of equal efficacy, therefore, requires fidelity in implementing those core components. This constitutes good scientific practice, but replication means, in effect, holding culture and local context constant—which is impossible. Measurement precision varies in all scientific work; there is no one scientific method; hypothetical constructs are hypothetical; scientific knowledge is evolving; facts are tentative; and the causal chain model is of limited application while complexity is the rule.

If programs are molar, practices are more molecular—skills, techniques, and strategies such as supportive, confrontational, nondirective, and so forth are based on theory and supported by practice evidence. This distinction helps to clarify the problem with generalizing model programs to diverse cultures and contexts. The primary means of introducing science-informed best practices into community- and culture-based programming is by professional training and mentoring in best practices.

The term "best practices" does in fact refer to practices in many nooks and crannies of health services. "Practices" are defined as routine business or professional activities, such as using a checklist in an operating room (Fixen et al., 2005; see Arriga et al., 2013). "Best" means that, based on scientific, practice, and cultural evidence, some practices are preferable. Continuous quality improvement is the ongoing process of discovering and applying best practices. A program manual will describe a number of best practices (item 5 in Fig. 2.2).

Kernels: Basic Units of Influence in Behavioral Health Services

There is a concept of science-based knowledge that is much more amenable to incorporation into locally and culturally based programming than practices and programs. Evidence-based *kernels* (Embry & Biglan, 2008) are more atomic than molecular practices and much more atomic than molar programs. Kernels are the unheralded active components of existing programs. Kernels, such as the ubiquitous "time out," are fundamental units of behavior-influencing techniques

having both empirical and theoretical bases. The four primary mechanisms of kernels are (1) providing consequences for behavior, (2) establishing antecedent stimuli for behavior, (3) altering people's relational framing about targeted behaviors, and (4) altering physiology that affects behavior. Kernels are specific to age groups. New or modified programs can be created by assembling groups of kernels. Since the kernels are evidence-based, the programs that incorporate them have a reasonable claim to efficacy. This fact provides a useful bridge between culture-based interventions and Western EBP. Instead of trying to adapt EBP, we can (1) innovate culture-based interventions and (2) identify and incorporate synergistic evidence-based kernels. Fifty-two examples of empirically supported kernels are given in Embry and Biglan (2008). This is a concrete contribution to creating evidence-informed programs in AI/AN communities.

Table 2.1 shows some examples of kernels with their empirical support: verbal praise (Leblanc, Ricciardi, & Luiselli, 2005; Lowe & McLaughlin, 1974; Marchant & Young, 2001; Marchant, Young, & West, 2004; Martens, Hiralall, & Bradley, 1997; Matheson & Shriver, 2005; Robinson & Robinson, 2000; Scott, Spender, Doolan, Jacobs, & Aspland, 2001), time out (Fabiano et al., 2004; Kazdin, 1980; Wolf, Risley, Johston, Harris, & Allen, 1967), and Turtle Technique (Heffner, Greco, & Eifert, 2003; Robin, Schneider, & Dolnick, 1976).

The concept of kernels is well supported by scientific evidence but has not been widely discussed or applied to the conceptualization or use of EBP. Kernels provide concrete, evidence-based steps that can be used for the manual (Fig. 2.2, item 5). Introducing these kernels into culture-based intervention is the least conflict-laden means of achieving evidence-informed programs in Native communities.

CONCLUSIONS

Large health disparities in AI/AN communities present an opportunity for behavioral health professionals to contribute greatly to the health of Native Americans. To seize upon this opportunity, it is necessary to understand and appreciate tribal worldview, epistemology, and healing practices. The same is true for working in all indigenous communities and, indeed, there are some general similarities worldwide: The practitioner always needs to understand and appreciate the target population. In fact, there are also some general commonalities (e.g., spirituality, placebo effects) among societies, indigenous and advanced.

TABLE 2.1 Selected Kernels

Kernel: Verbal Praise	
Description	*Behaviors affected*
Person or group receives spoken (or signed) recognition for engagement in target acts, which may be descriptive or simple acknowledgments	Cooperation, social competence, academic engagement/achievement, positive parent–child interactions or marital relations; better sales; reduced disruptive or aggressive behavior; reduced *DSM-IV* symptoms
Kernel: Time Out	
Description	*Behaviors affected*
Using timer, remove from natural reinforcement for 1 min for each year of age	Decreases noncompliance, argumentative behavior, and mood outbursts
Kernel: Turtle Technique	
Description	*Behaviors affected*
Using a turtle metaphor, child holds self, verbal frame, breathes through nose, and engages in subverbal or verbal self-coaching, with peer or adult reinforcement	Reduces arousal and aggression against peers or adults

We conclude that a certain attitude and protocol are essential to working in AI/AN communities. In this chapter, we have helped the reader to appreciate some of the limitations on our science-based body of knowledge and practice and to understand that best practices derive from multiple streams of evidence, including those that are science-, practice-, and culture-based. There is more than one way of knowing, which has an impact on what one refers and defers to during collaborative work. Even for those enlightened professionals already holding this philosophical and diplomatic view, it remains a task of skill and delicacy to put that respectful and encompassing attitude into practice in the field. *Faux pas* will happen, but sincere effort is noticed and appreciated, even when imperfect.

Beyond general respect and appreciation, cultural competence also requires boring down to a certain level of detail. We conclude that spirituality is a fundamental aspect of the Native American worldview. Spirituality means that the seen world is paralleled by and interwoven with an unseen one that influences etiology, outcomes, and practices—what causes things, what are the consequences of things, and what one does about it. There are quasireligious protocols—such as opening and closing prayers—related to the spiritual worldview, but more important is the spirituality precept itself. Illness and healing are seen through that prism. The fact that these precepts are conceptual, rather than positivistic facts or even hypothetical constructs, in no way diminishes their efficacy and importance.

In addition to prayers, the Western professional experiences other practices and protocols in Native communities not normally encountered in mainstream programs. Drumming, chanting, dancing, bundles of sacred objects, smudging, trances, medicine wheel, costumes, masks, honoring ceremonies, and other culture-specific components of traditional healing will become part of the partnering. It takes a little time, but the Western professional with a respectful attitude will become comfortable with these aspects of an effective partnership in AI/AN communities. These practices can be incorporated into treatment by referral to an appropriate provider or venue.

We conclude that a number of theories of action underlie healing practices in AI/AN communities. At this theoretical level there are notable commonalities with Western behavioral health strategies. Storytelling is how elders, healers, and others impart models for good living and problem resolution for individual Native Americans. Myths become a shared conceptual base for the society that can, for example, facilitate such healing practices as soul retrieval. Flight and loss of soul is understood to be the cause of some behavioral health disorders, and soul retrieval through trances and journeys into the spirit world is an important part of remediation. The retrieval service is provided by recognized and respected healers.

"Placebos" are not limited to just inert pills and deception; they are uses of the mind–body connection. The competent management of the placebo effect is a very powerful tool in the hands of Native American healers, who go to great length and sophistication to maximize the effect. Herbals and other substances with useful active ingredients have been identified in the natural environment over the millennia by Native Americans and are still used with beneficial effect.

The entire traditional healing enterprise in AI/AN communities involves teaching and learning processes with responsibilities for one and all, especially elders. Leaders (or funders or regulators) of healing in AI/AN communities need to recognize that fun and food are essential program material.

The high prevalence of behavioral health problems is attributable to social factors, the usual consequences of invasion, conquest, occupation, and oppression that have been visited upon all peoples at one time or another, but notably by advanced, Western nation-states upon indigenous peoples in the last 500 years or so. Despite major improvements in Western attitudes toward indigenous peoples, specific social factors are at work today, including deprivation of environmental resources, low socioeconomic status, dysfunctional political structures and leadership, damaged culture (which would otherwise guide and incentivize good ways of living), and racism. We conclude that effective behavioral health strategies need to encompass public health, community development, nation development, and cultural renaissance.

The merging of traditional with science- and practice-based practices has been helped along by the education, training, and mentoring of Native American professionals as well as by partnering with traditional healers. But capacity is still disproportionately limited in AI/AN communities, and professional work—education, training, mentoring, and

partnering—is aimed at capacity building. And capacity building has to be part of the continuous quality improvement effort.

We have tried logic models and conclude that they provide a helpful tool for bridging culture-, practice-, and science-based approaches to behavioral health services. The model presented in this chapter facilitates communication and exploration of cultural approaches in a format recognized by Western professionals. The logic modeling process also carries benefits recognized by Western professionals—conceptual exploration, development, and evaluation. We have concluded that another Western conceptual tool, kernels, also provides a very useful way of incorporating science-based knowledge into local and culture-based programming. While implementing EBP with fidelity creates a collision of cultures, the incorporation of the smallest units of science-based behavioral influence, the kernel, is synergistic, yielding scientific evidence-informed interventions.

With these attitudes and background information, Western professionals trained in EBP will collaborate successfully in AI/AN communities. Leaders in program improvement and administrative officials will have a better understanding of culture-based proposals and programming. This information also provides scientists with a perspective for studying culture-based interventions.

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NOTES

1. There are a number of names for our population of interest. We use "American Indian/Alaska Native," which is widely accepted.

2. We use "Native communities" synonymously with the legal term "Indian Country" as a way of recognizing the agency of communities and their members.

3. There are several ways of referring to scientific evidence-based programs. "Evidence-based programs and practices" is drawn from the frequently referenced National Registry of Evidence-Based Programs and Practices.

4. "Best practices" are what a well-educated and experienced member of the culture would regard as the preferable way of doing things.

5. EBP are offered as model programs and include supports for their implementation, including manuals, consultation, fidelity testing, and so forth (usually for sale). Replication of model programs is somewhat like establishing franchises, which involves some local ownership issues (matters of feeling and participation) as well as major, troublesome implementation issues usually attributed to flawed fidelity.

6. Sovereignty, consultation, and federal-government-to-tribal government relations are spelled out in U.S. and Canadian treaties, executive orders, and legal precedent. These legal instruments accord unique status and rights to tribes that are not accorded to minority groups in general, as well as placing limitations on nontribal governments over AI/AN matters and placing obligations on nontribal governments to support tribal resource needs (including health). Many member states of the United Nations have signed the Declaration of the Rights of Indigenous Peoples, encompassing land, identity, culture, language, employment, health, education, and self-determination.

7. NREPP uses a scale of quality of research different from the one used in this book. There are six criteria: reliability of measures, validity of measures, intervention fidelity, missing data and attrition, potential confounding variables, and appropriateness of analysis. NREPP reviewers use a scale of 0.0 to 4.0, with 4.0 being the highest rating given.

Levels on evidence mentioned in this chapter are as used throughout this book

Cite page number in book where "levels" are defined

8. The original, tested model program itself with its unique personnel, subjects, and conditions, is locally and culturally based.

9. Scientific methods are not limited just to "experiments" or "randomized clinical/controlled trials" but, rather, include any available method that increases knowledge and certainty of knowledge.

10. Misclassification of ethnicity and misclassification of cause of morbidity or mortality are significant contaminants of data affecting etiologic interpretations.

11. *Target-tropism* is the phenomenon of behavior automatically orienting to the identified target. It is

better to identify opportunities for improvement rather than problems wherever possible.

12. There are two Gathering of Native Americans (GONA) programs. One is a powwow supported by a dedicated organization. The GONA referred to here is a training program recently supported by the Native American Center for Excellence operated by Kauffman & Associates, Inc., and funded by SAMHSA. Printed material can be difficult to find as it has been moved about from site to site.

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3

Nonpharmacologic Treatments for Childhood Attention-Deficit/ Hyperactivity Disorder and Their Combination with Medication

Linda J. Pfiffner
Lauren M. Haack

The high prevalence, serious functional impairments, and chronic nature of attention-deficit/ hyperactivity disorder (ADHD) have fueled the development of treatments for the disorder for more than five decades. Behavioral interventions have been the most well-researched, consistently applied, and effective of the nonpharmacologic treatments for ADHD. This chapter begins with an update on the latest research related to the phenomenology and associated impairments of ADHD, followed by a summary of the latest research on behavioral interventions, applying rigorous typology standards for clinical trials. We consider multiple outcome domains and cross-setting treatment effects in view of the far-reaching impact of the disorder. We also review the latest research on incremental effects of combined behavioral and medication treatments, given the limited capacity of either treatment to normalize functioning or substantially alter long-term outcomes. The current limited effects of other nonpharmacologic treatments, including cognitive training and neurofeedback, are also discussed. While evidence supporting behavioral interventions continues to mount, important areas for future research include the need to better tailor treatments to nonresponders and partial responders, improve accessibility to broader populations, and foster treatment innovations to improve long-term outcomes.

DESCRIPTION OF ADHD

ADHD is one of the most common and well-researched childhood disorders. Over the past thirty years, the disorder's name and diagnostic criteria have undergone a number of changes in parallel with the refinement of the conceptualization of the disorder. In the most recent revision of the *Diagnostic and Statistical Manual for Mental Disorders* (5th ed., *DSM-5*; American Psychiatric Association [APA], 2013), the symptoms of ADHD have remained the same as in the *Diagnostic and Statistical Manual for Mental Disorders* (4th ed., *DSM-IV*; APA, 1994). Specifically, ADHD is characterized by a constellation of inattention and/or hyperactivity/impulsivity symptoms. In addition, because these kinds of problems can be normative during childhood, diagnostic criteria specify that they must occur with sufficient frequency and severity to compromise daily functioning in at least two settings, usually home and school (see *DSM-5* Diagnostic Criteria for Attention-Deficit Hyperactivity Disorder [APA, 2013]). ADHD is classified according to the pattern of elevations in the two symptom groupings. In *DSM-IV*, these were

referred to as subtypes (i.e., predominantly inattentive, predominantly hyperactive, or combined), but in *DSM*-5, these types are now referred to as "presentations." The criteria for presentation are the same as for type and reflect the predominant pattern of symptoms at the time of the evaluation. The change in terms reflects research showing that the types are often unstable during development (Willcutt, 2012), with the implication that current symptom presentation may change over time. Controversy continues over the quantitative versus qualitative distinction between the types/presentations (e.g., Milich et al., 2001). Regardless, studies reveal a number of differences between the two presentations that should be considered in treatment planning, including differences in cognitive/attention-deficit profiles (sluggish cognitive tempo; slow processing speed), gender distribution, comorbid disorders, social impairments, and some aspects of treatment response (Bauermeister et al., 2005; Milich et al., 2001).

Three additional changes have been made to the ADHD diagnostic criteria in *DSM*-5 (APA, 2013). First, the age-of-onset criterion was broadened from "before the age of 7" to "before the age of 12." This decision was based on difficulty specifying exact age of childhood onset retrospectively and data showing similar impairment for youth identified with symptoms before seven and those identified after seven but before the teenage years (Willcutt, 2012). Second, the symptom count threshold was reduced for individuals age seventeen and older, due to data showing continued impairment despite some reductions in symptom presence over development (Tannock, 2013). Third, the *DSM*-5 includes three severity modifiers (mild, moderate, severe) to reflect the number of symptoms and level of impairment. These changes to *DSM*-5 are unlikely to alter the prevalence, correlates, or treatment response of ADHD for most children and adolescents significantly; thus, the ADHD literature based on *DSM-IV* criteria should apply to the *DSM*-5 presentations. We will use the *DSM*-5 terminology throughout this chapter, recognizing, however, that the studies were conducted with youth classified by the *DSM-IV* types.

Prevalence rates for ADHD in children and adolescents range from 5.9% to 7.1% when standardized diagnostic procedures are followed, based on a recent meta-analytic review, with more boys affected than girls (Willcutt, 2012). However, community rates established from a national survey conducted by the Centers for Disease Control and Prevention are higher (according to parent report, 11% of youth four to seventeen years of age have ever been diagnosed with ADHD), and regional and cultural variations in prevalence have been reported, with the highest rates occurring among Caucasians relative to other groups and in the South and Midwest, with rates close to 15% (Visser et al., 2014). Variability in prevalence appears to be mostly explained by differences in diagnostic algorithms and methodology (Willcutt, 2012).

Impairment for youth with ADHD typically occurs across most domains of functioning. Academic problems are pervasive for all ADHD presentations (DuPaul et al., 2004). Students with ADHD consistently exhibit lower rates of on-task behavior during instruction and independent work periods that are likely to underlie a number of adverse academic outcomes (Imeraj et al., 2013). Crucially, classwork and homework completion, test and report card grades, as well as tests of academic achievement are significantly lower among youth with than those without ADHD (Langberg et al., 2011; Power et al., 2006; Schultz et al., 2009). As students with ADHD proceed through schooling, prospective follow-up studies show they are at considerable risk for placement in special education classrooms, grade retention, school failure, early dropout, and juvenile delinquency (Barkley, 2006; Barkley et al., 1990; Fischer et al., 1993), and girls in particular are at increased risk for self-harm and suicide (Hinshaw et al., 2012).

ADHD symptoms also contribute to interpersonal problems with peers, parents, and teachers (Mikami, 2010), problems that can be exacerbated by associated aggression, argumentativeness, disruptiveness, and lack of self-control (Pfiffner et al., 2000). They have less sustained social interaction and are less actively engaged in reciprocal play (Bellanti & Bierman, 2000; Mikami et al., 2007), and their peer interaction styles tend to be overly negative (Mikami, 2010). At least half of those with ADHD are rejected by their peers, and many others, especially those with the inattentive presentation, are neglected or ignored by their peer group; most have few friendships (Pfiffner et al., 2000). ADHD also affects family functioning, which is characterized by parent–child conflict and parental stress (Johnston & Mash, 2001). Parents of children with ADHD demonstrate higher levels of negative and ineffective parenting (e.g., power assertive, punitive, inconsistent) and lower levels of positive or warm parenting relative to parents of comparison children

(Gerdes et al., 2003; Johnston & Mash, 2001). These parenting styles predict poor academic outcomes, peer relations, and social skills and aggressive behavior and have an adverse impact on school success overall (Hinshaw et al., 2000; Kaiser et al., 2011).

Current conceptualizations of ADHD implicate multiple, rather than singular, neuropsychological weaknesses. That is, no specific weakness (e.g., overall executive functions, delay aversion, motivational dysfunction, response variability, processing speed) has been found to be either a necessary or sufficient cause of the disorder (Willcutt & Bidwell, 2011), and recent theoretical models propose that ADHD arises from weaknesses in multiple cognitive domains. While multiple etiologies may result in ADHD, heritability is substantial and genetic and neurologic factors are considered leading causes (Nigg, 2006). However, biologic markers are yet to be reliably identified, and diagnosis continues to be based on clinical history, behavioral observations of parents and teachers, and consideration of comorbid conditions. Parenting and teaching practices are not causal, but social environmental factors can influence severity, extent of impairment, and comorbid problems. The latter include oppositional defiant and conduct disorders (often above 50%), as well as anxiety disorders (25%) and depressive disorders (29% to 45%) (Barkley, 2006; Jarrett & Ollendick, 2008; Spencer, Biederman, & Mick, 2007). Even if full *DSM* criteria are not met for a comorbid disorder, subclinical levels of difficulty are often present.

In recent years, the societal cost of ADHD has become increasingly clear. In a recent review of nineteen studies, Doshi and colleagues (2012) estimated that the national annual incremental costs of ADHD in children range from $38 to $72 billion. For children the largest cost categories are health care ($21 to $44 billion) and education ($15 to $25 billion). These costs, along with the serious and chronic impairment across most domains of daily functioning, underscore the need for effective treatments for this disorder.

CONCEPTUAL UNDERPINNINGS OF BEHAVIORAL INTERVENTIONS

For the past five decades, behavioral interventions have been the most well-researched and consistently implemented nonpharmacologic, psychosocial treatments for ADHD. Based on social learning theory, behavioral approaches for ADHD emphasize the importance of environmental/social contingencies in fostering and maintaining problem behaviors (i.e., "contingency theory" [Patterson, 1982]) and also incorporate modeling and imitation and cognitive factors (e.g., cognitive appraisals and attributions). Situational factors are conceptualized as key determinants of immediate behaviors and impairments regardless of the underlying neurobiologic propensity. Behavioral interventions typically include a "functional behavior analysis," which involves specifying behaviors (positive behaviors to increase or negative behaviors to decrease) and then identifying each behavior's antecedents (variables setting the stage for or preceding the behavior) and consequences (variables maintaining the behavior). Based on this analysis, specific strategies for modifying antecedents and consequences are selected for a behavior intervention plan with the goal of reducing problem behavior and promoting desired behavior. Generally, the behavioral approach to intervention selects target behaviors for treatment that cause impairment in daily living (e.g., academic, social behavior) rather than targeting diagnostic symptoms per se, although it is important to note that these interventions often do have powerful direct and indirect effects on diagnostic symptoms. More recently, the behavioral approach to treatment has been expanded to include child skills training, often imbedded within cognitive-behavioral strategies (Villodas et al., 2013). These interventions are based on a skill-deficit model and posit that directly teaching the skills and strategies will improve performance in daily academic and/or social activities.

Recent studies on responses of youth with ADHD to rewards and punishments underscore the utility of behavioral interventions for this population. These studies suggest that ADHD is associated with neurally based motivational systems that respond poorly to usual contingencies from parents and teachers (i.e., a reduced response to delayed, inconsistent, or weak contingencies) but well to immediate, salient, and consistent contingencies (Pfiffner, 2008; Sonuga-Barke, 2011). Specifically, children with ADHD appear to have a higher threshold for rewards (Haenlein & Caul, 1987) and are less responsive to partial reinforcement (Parry & Douglas, 1983), delayed reinforcement (Sonuga-Barke, 2005), and signs of punishments or loss of rewards (Quay, 1997) than children without ADHD. Such reward-related deficits may relate, at a neural level, to a lack of receptors for dopamine

in key brain tracts (Volkow et al., 2009). Behavioral interventions that stress immediate, predictable, and salient rewards, appropriate consequences, consistent routines, and clearly structured rules and expectations are well suited to address these motivational problems.

OUTCOMES OF NONPHARMACOLOGIC TREATMENT STUDIES

Before describing the current status of evidence, we briefly review the findings of the preceding review, which covered the years 1980 to the mid-2000s (see Hinshaw et al., 2007). In that review, behavioral interventions were divided into two categories: direct contingency management and clinical behavior therapy. Direct contingency management included studies of intensive reward and punishment procedures in specialized treatment facilities or demonstration classroom or summer treatment programs. Clinical behavior therapy procedures involved consultation with parents or teachers, who then implemented the behavior management strategies in their usual environments. Direct contingency management, appraised mostly through single-case experimental designs, showed large effects while the contingencies were administered but little generalization to nontreated settings. Studies of clinical behavior therapy showed significant effects as well, but the strongest outcomes were mostly based on parent and teacher report rather than independent observations, leaving open the possibility of informant bias as an explanatory factor. Behaviorally oriented social skills training showed initial promise, but not consistently so across studies. Hinshaw and colleagues (2007) also reported outcomes from several investigations using a combination of direct contingency management and clinical behavior therapy, but effects on symptom reduction were not as great in comparison to effects of medication. Furthermore, they reported that combined intensive behavioral intervention and medication did not always yield greater effects than medication alone, although they did appear to more consistently yield normalization of behavior patterns and may have had a somewhat broader impact on impairment domains than medication alone. In addition, combination treatments were reported to be especially useful for cases with ADHD and comorbid conditions. The need for improving the impact, scope, and long-term effects of behavioral interventions was stressed since existing psychosocial treatments fell short of clinically sufficient benefit. In addition, greater use of objective measures of outcome was recommended. There was also a call to develop other types of nonpharmacologic interventions, drawing upon underlying mechanisms of the disorder and/or impairments.

A number of important advances in these areas have been made since the last review. In a recent meta-analysis, Fabiano and colleagues (2009b) reported large between-group effect sizes (d = .83) for behavioral interventions when collapsed across outcome measures. The largest effects were seen for parent-rated functional impairment, teacher-rated ADHD symptoms, and academic productivity. Although a different meta-analysis reported smaller effects for behavioral interventions (Sonuga-Barke et al., 2013), the criteria for study inclusion in the latter review were quite restricted (e.g., only those with an ADHD symptom outcome and blinded assessment), and as a result much of the literature supporting behavioral intervention effects on functional impairment, arguably the most clinically important outcomes, was not considered.

For this update, we include randomized controlled trials (RCTs) published since the last review (dates: 2007 through 2013) that meet criteria for either type 1 or 2 using the standards-of-proof framework for this volume. We also include studies of comparisons and combinations of behavioral interventions and medication using single-case experimental designs (e.g., reversal or multiple-baseline). Although the latter studies do not meet criteria specified in the standards-of-proof framework, they do include rigorous control for nontreatment factors and are uniquely informative about multimodal treatment effects.

We have modified the classifications of behavioral treatments used in the previous edition of this chapter to reflect advances in research that conceptualize treatment by setting and agent of change and for closer consistency with other meta-analyses and reviews (e.g., Evans et al., 2013; Fabiano et al., 2009b; Pelham & Fabiano, 2008). We divide interventions according to the focus of the intervention as follows: behavioral parent training (BPT), behavioral classroom management (BCM), child skills training, behavioral multicomponent interventions, and multimodal treatment combining behavioral interventions and medication. In addition, a new category for cognitive and neurofeedback studies has been added, given

the recent publication of controlled outcomes studies for these treatments.

Table 3.1 presents key features of RCTs of behavioral interventions with diagnosed cases of ADHD completed between 2007 and 2013. For each study, we highlight participants, study design and treatment description, outcome domains and raters, main findings, and effect size/clinical significance. Studies of other nonpharmacologic treatments are not included in the table, given the sparse evidence for their efficacy. Following our review of outcome studies within each treatment category, we summarize overall findings and limitations and provide recommendations for future research.

Behavioral Parent Training

BPT has been confirmed as an efficacious treatment based on three separate reviews since 1998 (Evans et al., 2013; Pelham & Fabiano, 2008; Pelham et al., 1998). BPT directly targets negative and ineffective parenting, which is a well-documented correlate of ADHD. In this intervention, a clinician works with parents either individually or in groups to provide psychoeducation about ADHD, to teach parents behavior modification principles and strategies, and to adapt these strategies to individual families' home environments. Most BPT curricula specify a common set of skills over the course of eight to sixteen sessions focused on (1) improving parent–child relationships through increasing quality time together; (2) increasing positive behaviors through the use of effective instructions and rewards such as desirable activities and privileges, specific praise, and other forms of positive reinforcement; and (3) reducing problem behaviors by implementing prudent corrective statements and time-out and response-cost procedures or by employing planned ignoring to curtail attention-seeking behaviors. Parents learn to use strategies taught in sessions to alter both antecedents and consequences of problem behaviors in commonly challenging situations such as morning or evening routine, homework completion, and/or independence in other home-based tasks.

Since the last version of this chapter, six additional RCTs have been added to the scientific evidence base for BPT with diagnosed cases of ADHD. New studies are largely adaptations of existing delivery models that broaden the effects of training by increasing access and/or reaching individuals who appear to be less responsive to parent training, including those from economically or socially disadvantaged backgrounds or those who have their own mental health issues. Chacko and colleagues (2009) adapted BPT for single mothers (Strategies for Enhance Positive Parenting [STEPP]) by adding to standard BPT strategies to improve motivation to engage in the treatment, increasing the length of treatment sessions, addressing practical barriers (e.g., childcare), and incorporating staff modeling of the behavioral strategies. This approach improved attendance, engagement, and satisfaction with treatment relative to traditional BPT. STEPP also resulted in greater improvements in oppositional defiant disorder symptoms, parent–child and family-related impairment, and observations of parenting relative to traditional BPT and outperformed a waitlist control on these measures at posttreatment but not at follow-up.

BPT also has been adapted for fathers by integrating activities appealing to fathers (e.g., sports) into the training curriculum (Chacko et al., 2009; Fabiano et al., 2009a). The intervention, referred to as COACHES, includes group BPT for fathers followed by soccer practice during which fathers coached their children using their new skills and received feedback from counselors. Results show that the COACHES program resulted in similar effects as standard BPT on ADHD-related child outcomes. However, fathers who received COACHES relative to BPT had better attendance, less dropout, better homework compliance, and greater satisfaction with treatment, all indicating greater engagement with the father-focused treatment. In a second study, COACHES resulted in greater improvement on unblinded observations of fathers' use of praise and negative talk and paternal reports of child behavior problems relative to a waitlist control, with evidence of maintenance at follow-up (Fabiano et al., 2012).

Adaptations to BPT have also been developed for depressed mothers by adding cognitive-behavioral strategies to treat the mother's depressive symptoms (Chronis-Tuscano et al., 2013). This is particularly relevant for mothers of children with ADHD, who are more likely to experience depression than are parents of control children (Johnston & Mash, 2001). In comparison to traditional BPT, the enhanced BPT (Integrated Parenting Intervention) resulted in greater improvement at posttreatment on observations of negative parenting and child deviance as well as

TABLE 3.1 Findings From Behavioral Clinical Trials From 2007 to 2013

Behavioral Parent Training (BPT) Clinical Trials

Study	*Participants*	*Study Design and Nonpharmacologic Treatment Description*	*Outcome Domains & Raters**	*Main Findings+*	*Effect Size and Clinical Significance*
Chacko et al., 2009	N = 120 Ages 5-12 Dx: *DSM-IV* ADHD	Type 2 between-subject waitlist control design 1. Enhanced BPT for single mothers (9 weeks: STEPP) 2. Traditional BPT (9 weeks) 3. Waitlist Control	A. ADHD symptoms (P) B. ODD symptoms (P) C. Functional impairment (P) D. Parenting behavior (O) E. Parent stress (P) F. Parent depression	A. 1 = 2 = 3 B–D. 1 & 2 > 3 at post only; 1 > 2 at post only E. 1 > 2 > 3 at post only F. 1 = 2 = 3	Small to large effect sizes for significant contrasts indicating improvement after 1 & 2 A–E. 1 > 2 > 3 for normalization, although the difference was not significant
Chronis-Tuscano et al., 2013	N = 98 Ages 6–12 Dx: *DSM-IV* ADHD	Type 1 between-subject waitlist control design 1. Enhanced BPT for depressed mothers (14 weeks: IPI-A) 2. Traditional BPT (14 weeks)	A. Disruptive behavior disorder symptoms (P) B. Functional impairment (P) C. Parent depression (P) D. Parenting behavior (O*) E. Child behavior (O*)	A. 1 > 2 at FU only B, C. 1 > 2 at post and FU D, E. 1 > 2 at post only	Small to large effect sizes for significant contrasts A & B. 1 > 2 for reliable improvements D. 1 > 2 for normalization
Fabiano, Pelham, et al., 2009	N = 75 Ages 6–12 Dx: *DSM-IV* ADHD	Type 2 between-subject waitlist control design 1. BPT for fathers (8 weeks: COACHES) 2. Traditional BPT (8 weeks)	A. ADHD symptoms (P) B. ODD symptoms (P) C. Functional impairment (P) D. Social functioning (P)	A, B, D. 1 = 2 indicating improvement C.1 > 2 as rated by fathers; 1 = 2 as rated by mothers	N/A
Fabiano et al., 2012	N = 55 Ages 6–12 Dx: *DSM-IV* ADHD	Type 2 between-subject waitlist control design 1. BPT for fathers (8 weeks COACHES) 2. Community control *Note*: 46% of treatment group & 60% of community control using medication; no differences emerged	A. Behavior problems (P) B. Parenting behavior (O)	A. 1 > 2 at post only as rated by fathers; 1 = 2 as rated by mothers B. 1 > 2 at post and FU	A. 1 = 2 for normalization of problem behaviors

McGrath et al., 2011	N: 72 Ages 8–12 Dx: *DSM-IV* ADHD	Type 2 between-subject community control design 1. BPT (12 sessions via telephone: Strongest Families program) 2. Community control	A. ADHD diagnosis (P) B. ADHD symptoms (P)	A & B. 1 > 2 at 240- and 365-day but not at 120-day assessment	N/A
Mikami et al., 2010	N: 62 Ages 6–10 Dx: *DSM-IV* ADHD (42 of 62 ADHD-C; 40 of 62 medicated)	Type 1 between-subject community control design 1. BPT (8 sessions Parent Friendship Coaching) 2. Community control	A. Social impairment (P,T*) B. Social acceptance (T*) C. Parenting skills (O*) E. Parenting behavior (O*)	A. 1 > at post and 1-month FU (P only) B–D. 1 > 2	Small to large effect sizes for significant contrasts
Behavioral Classroom Management (BCM) Clinical Trials					
Fabiano et al., 2010	N = 63 Ages 6–12 Dx: *DSM-IV* ADHD; 15% inattentive type, 85% combined type	Type 1 between-subject community control design 1. BCM (6 weeks Daily Report Card) 2. Community control *Note*: 46% of treatment group & 60% of community control using medication; no differences between groups emerged	A. Academic performance (T; O) B. Academic achievement testing C. ADHD symptoms (T) D. ODD & CD symptoms (T) E. IEP goals F. Classroom behavior (O*) G. Student–teacher relationship (T) H. Functional impairment (T)	A. 1 > 2 for academic productivity and success only B, C. 1 = 2 D–F. 1 > 2 G, H. 1 = 2	Medium effect sizes for significant contrasts A. 1 > 2 for normalization of problem behaviors D. 1 > 2 for normalization of ODD/CD symptoms
Mikami et al., 2013	N: 24 Ages 6.8–9.8 Dx: *DSM-IV* ADHD	Type 2 between-subject repeated measures crossover design 1. Enhanced BCM (4 weeks Enhanced Classroom Contingency System focused on Social Skills: MOSAIC) 2. Traditional BCM (4 weeks Traditional Classroom Contingency System focused on Social Skills: COMET)	A. Peer acceptance (T) B. Social functioning (O*) C. Problem behaviors (T) D. ODD & CD symptoms (T)	A. 1 > 2 B–D. 1 = 2	Large effect sizes for significant contrasts

(*continued*)

TABLE 3.1 (continued)

Study	*Participants*	*Study Design and Nonpharmacologic Treatment Description*	*Outcome Domains & Raters**	*Main Findings+*	*Effect Size and Clinical Significance*
Murray et al., 2008	N = 24 Grades K–5 Dx: *DSM-IV* ADHD *Note*: partial randomization due to school year end and recruitment timing	Type 2 between-subject community control design 1. BCM (4 months Daily Report Card) 2. Community control *Note*: most participants were already receiving ADHD treatment, such as medication, IEP/504s, and individual therapy. No participants in group 2 were receiving a DRC, although some had a classroom behavior plan.	A. Academic performance (T) B. Classroom impairment (T)	A. 1 > 2 for academic skills and total academic performance B. 1 = 2, with both groups indicating improvement	A. Large effect sizes for significant contrasts
Behavioral Child Skills Training (BCS) Clinical Trials					
Abikoff et al., 2013	N = 158 Ages 8–11 Dx: *DSM-IV* ADHD	Type 2 between-subject waitlist control design 1. BCST (20 sessions Organizational Skills Training: OST) 2. BMC (20 sessions Parents and Teachers Helping Kids with Organization: PATHKO) 3. Waitlist control	A. Organizational skills (P,T) B. Academic functioning (T) C. Homework problems (P) D. Family functioning (P) E. School attitude (P,T)	A. 1 > 2 > 3 at post and FU (P), 1 = 2 > 3 at post and FU (T) B–D. 1 = 2 > 3 E. 1 = 2 = 3	Medium to very large effect sizes for significant contrasts; 60% of children in 1 & 2 normalized in organization vs. 3% in 3
Langberg et al., 2012	N: 47 Ages 11–14 Dx: *DSM-IV* ADHD	Type 2 between-subject waitlist control design 1. BCST (16 sessions Organization Skills Training: HOPS) 2. Waitlist control *Note*: Majority of participants receiving ADHD medication and/or academic services/accommodations	A. Organizational skills (P,T) B. Homework problems (P,T) C. ADHD symptoms (P,T) D. School grades	A. 1 > 2 at post and 3 month FU (P only) B. 1 > 2 at post and 3-month FU (P only) C. 1 > 2 at post only (P only) D. 1 > 2	Large to very large effect sizes for significant contrasts

Behavioral Multicomponent (BMC) Clinical Trials

Evans et al., 2011	N = 49 Ages 10–13 Dx: *DSM-IV* ADHD	Type 2 between-subject community control design 1. BMC (6 months Challenging Horizons; incorporates BCST, BPT, & family meetings) 2. Community control	A. ADHD symptoms (P,T) B. Functional impairment (P,T) C. Academic performance (T) D. School grades	A. 1 > 2 for HI symptoms (P) B. 1 > 2 (T) C. 1 > 2 for Language Arts & Social Studies (T) D. 1 = 2	Medium effect sizes for significant contrasts
Kern et al., 2007	N = 135 Ages 3–5 Dx: *DSM-IV* ADHD	Type 2 between-subject design 1. BMC (18 months incorporating BPT and assessment-based intervention in the home and class) 2. BPT (18 months)	A. ADHD symptoms (P,T) B. Social functioning (P,T) C. Academic performance (T) D. Academic achievement testing	A–D. 1 = 2 with both indicating significant improvement	N/A
Meyer & Kelley, 2007	N = 42 Ages 11–14 Dx: *DSM-IV* ADHD combined type	Type 2 between-subjects waitlist control design 1. BPT (Parent Monitoring Group with children present) 2. BCST (Self-Monitoring Group with parents present) 3. Waitlist control	A. Homework problems (P,T) B. Classroom behavior (T)	A. 1 & 2 > 3 at post and FU B. 1 = 2 = 3	N/A
Pfiffner et al., 2007	N: 69 Ages 7–11 Dx: *DSM-IV* ADHD inattentive type	Type 2 between-subject community control design 1. BMC (12 weeks incorporating BPT, BCST, and BCM: Child Life and Attention Skills Program) 2. Community control	A. ADHD-I symptoms (P,T) B. Sluggish cognitive tempo symptoms (P,T) C. Social functioning (P,T) D. Organizational skills (P,T) E. Life skills (C) F. Functional impairment (P,T)	A&F. 1 > 2 at post and FU B–E. 1 > 2 at post indicating maintenance to FU	Medium to large effect sizes for all significant contrasts

(*continued*)

TABLE 3.1 (continued)

Study	*Participants*	*Study Design and Nonpharmacologic Treatment Description*	*Outcome Domains & Raters**	*Main Findings+*	*Effect Size and Clinical Significance*
Pfiffner et al., 2014	N: 199 Ages 7–11 Dx: *DSM-IV* ADHD inattentive type	Type 2 between-subject community control design 1. BMC (12 weeks incorporating BPT, BCST, and BCM: Collaborative Life Skills Program) 2. BPT (12 weeks) 3. Community control	A. ADHD-I symptoms (P,T) B. Organizational skills (P,T) C. Social functioning (P,T) D. Functional impairment (P,T)	A. 1 = 2 > 3 at post and 1 > 3 at FU (P); 1 > 2 > 3 at post (T) B. 1 > 2 > 3 at post and 1 > 2 = 3 at FU (P); 1 > 2 = 3 at post (T) C. 1 > 3 at post (P); 1 > 2 = 3 (T) D. 1 = 2 > 3 at post and FU (P); 1 > 2 = 3 at post (T)	Medium to very large effect sizes for all significant contrasts
Power et al., 2012	N: 199 Grades 2–6 Dx: *DSM-IV* ADHD	Type 2 between-subject placebo control design 1. BMC (12 weeks incorporating BPT and BCM: Family School Success Program) 2. Placebo control (nonspecific ADHD support group)	A. Parent involvement (P,T) B. Homework problems (P,T) C. Parent–child relationship (P) D. ADHD & ODD symptoms (P,T) E. Academic performance (T)	A. 1 > 2 at post (P & T) and FU (T only) B. 1 > 2 at post (P & T) and FU (P only) C. 1 > 2 at post and FU f D,E. 1 = 2	Large effect sizes for significant contrasts
Seeley et al., 2009	N: 42 Ages 6–10 Dx: *DSM-IV* ADHD (24% IA, 52% HI, 24% CT)	Type 2 between-subject community control 1. BMC 3 months incorporating BPT and BCM: First Steps to Success) 2. Community control	A. ADHD symptoms (P, T) B. ODD symptoms (T) C. Social functioning (P,T) D. Academic performance (T) E. Classroom behavior (O)	A–E. 1 > 2 at post with the exception of parent-rated social functioning	A. Medium to very large effect sizes for significant contrasts

Webster-Stratton et al., 2011	N: 99 Ages 4–6 Dx: ADHD hyperactive/impulsive and combined type only	Type 1 between-subject waitlist control design 1. BMC (20 weeks incorporating BPT and BCST: Incredible Years) 2. Waitlist control	A. Child attention & behavior problems (P,T) B. Social functioning (P) C. Parenting behavior (O) D. Child behavior (O) E. Classroom behavior (O*) F. Parent functioning (P) G. Child problem solving and feelings (C)	A–G. 1 > 2	N/A
Multimodal Clinical Trials					
Jensen et al., 2007	N = 485 Ages 7–9.9 at baseline Dx: *DSM-IV* ADHD combined type	Type 2 between-subjects multimodal community control design 1. Methylphenidate + BMC incorporating 35 sessions BPT, 8 weeks BCST (Summer Treatment Program), 12 weeks BCM (half-time paraprofessional aide in the classroom and school-based teacher consultation) 2. BMC only 3. Methylphenidate only 4. Community control	A. ADHD symptoms and diagnostic status (P,T) B. ODD symptoms and diagnostic status (P,T) C. Functional impairment (P,T) D. Academic achievement testing E. Social functioning (P,T)	Unlike the 24-month FU, at 36 months: A–E. 1 = 2 = 3 = 4	N/A
Langberg et al., 2010	N = 579 Ages 7–9.9 at baseline Dx: *DSM-IV* ADHD combined type	Type 2 between-subjects multimodal community control design 1. Methylphenidate + BMC incorporating 35 sessions BPT, 8 weeks BCST (Summer Treatment Program [STP]), 12 weeks BCM (half-time paraprofessional aide in the classroom and school-based teacher consultation) 2. BMC only 3. Methylphenidate only 4. Community control	A. Homework problems (P)	A. 1 & 2 > 3 & 4 Moderators: Parent ratings of initial ADHD symptom severity	Medium effect sizes for significant contrasts

(*continued*)

TABLE 3.1 (continued)

Study	*Participants*	*Study Design and Nonpharmacologic Treatment Description*	*Outcome Domains & Raters**	*Main Findings+*	*Effect Size and Clinical Significance*
Molina et al., 2007	N = 579 Ages 7–9.9 at baseline Dx: *DSM-IV* ADHD combined type	Type 2 between-subjects multimodal community control design 1. Methylphenidate + BMC incorporating 35 sessions BPT, 8 weeks BCST (Summer Treatment Program [STP]), 12 weeks BCM (half-time paraprofessional aide in the classroom and school-based teacher consultation) 2. BMC only 3. Methylphenidate only 4. Community control	A. Antisocial behavior (P) B. Substance use (P,C)	A. 1 = 2 = 3 = 4 at 12, 24, 36 months B. 1 & 2 > 3 & 4 at 36 months	N/A
Molina et al., 2009	N = 436 Ages 7–9.9 at baseline Dx: *DSM-IV* ADHD combined type	Type 2 between-subjects multimodal community control design 1. Methylphenidate + BMC incorporating 35 sessions BPT, 8 weeks BCST (Summer Treatment Program [STP]), 12 weeks BCM (half-time paraprofessional aide in the classroom and school-based teacher consultation) 2. BMC only 3. Methylphenidate only 4. Community control	A. ADHD symptoms and diagnostic status (P,T) B. ODD symptoms and diagnostic status (P,T) C. Antisocial behavior (P,C) D. Functional impairment (P,T) E. Social functioning (P,T O) F. Academic achievement testing G. Comorbid mood disorders (P,C) H. Service use (P)	Similar to 36-month FU, at 6- and 8-year FU: A–F. 1 = 2 = 3 = 4 G. 2 > 1 = 3 = 4 for absence of anxiety disorder diagnoses at 6-year FU only H. 1 > 2 for less use of school services at 6-year FU only	N/A
Van der Oord et al., 2007	N = 50 Ages 8–12 Dx: *DSM-IV* ADHD	Type 2 between-subject multimodal design 1. Methylphenidate + BMC (10 weeks incorporating BPT, BCST, and BCM) 2. Methylphenidate only	A. ADHD symptoms (P,T) B. ODD & CD symptoms (P,T) C. Social functioning (P,T) D. Parent stress (P) E. Child self-worth and anxiety (C)	A–E. 1 = 2	A–E. Large effect sizes from pre to post in both groups

Van den Hoofdakker et al., 2007	N = 94 Ages 4–12 Dx: *DSM-IV* ADHD	Type 2 between-subject multimodal design 1. BPT (12 sessions) + routine clinical care (psychiatry care as usual, including medication and family therapy/support as needed) 2. Routine clinical care control	A. ADHD symptoms (P) B. ODD/CD symptoms (P) C. Internalizing symptoms (P) D. Parent stress (P)	A&D. 1 = 2 B&C. 1 > 2 at post and 6-month FU	A–C. Medium to very large effect sizes for significant contrasts
Wells et al., 2006	N = 579 Ages 7–9.9 at baseline Dx: *DSM-IV* ADHD combined type	Type 1 between-subjects multimodal community control design 1. Methylphenidate + BMC incorporating 35 sessions BPT, 8 weeks BCST (Summer Treatment Program [STP]), 12 weeks BCM (half-time paraprofessional aide in the classroom and school-based teacher consultation) 2. BMC only 3. Methylphenidate only 4. Community control	A. Parenting behavior (O*)	A. 1 > 3 = 4	Small to medium effect sizes

P = Parent, T = Teacher, C = Child, O = Observation; FU = follow-up.; IA = Predominantly Inattentive; HI = Predominantly Hyperactive/Impulsive; CT = Combined Type; ODD = Oppositional Defiant Disorder; CD = Conduct Disorder.

> indicates greater improvement for outcome domain.

* indicates rater(s) blind to treatment condition.

+Unless specifically noted, results reflect all measures and raters for each outcome.

ratings of impairment; group differences in maternal depressive symptoms and child disruptive behavior and impairment were also observed at follow-up.

One additional study addressed logistical barriers associated with parent attendance at sessions. McGrath and colleagues (2011) adapted BPT for telephone delivery. In this study, handouts and videos were provided for parents to view at home and twelve forty-minute telephone sessions were conducted to review the content. Results at eight-month and one-year follow-ups showed that the telephone format outperformed a community control in terms of ADHD symptom reduction (no other outcomes were assessed), and families were very satisfied with their telephone coaches.

In addition to these adaptations, BPT has been expanded beyond improving home behavior and parent–child relationships to improving friendship problems in an innovative approach developed by Mikami and colleagues (2010). This approach is supported by research showing that parents may contribute to their children's peer relationship problems by failing to facilitate successful playdates for their children, displaying more criticism during their child's peer interaction, and modeling fewer successful social skills (Mikami, 2010). The Parental Friendship Coaching (PFC) intervention includes eight ninety-minute sessions focused on teaching parents how to teach their children to interact successfully with peers during a playdate. Also covered are behavioral interventions and collaborative problem solving between parents and children before and after playdates. Relative to a community control group, PFC predicted improvements in children's social skills and friendship quality on playdates as reported by parents, and peer acceptance and rejection as reported by teachers unaware of treatment status. PFC also predicted increases in blinded observations of parenting practices, including facilitation of peer interactions and reductions in criticism, which had been taught during the treatment sessions and which mediated the improvements in children's peer relationships. Notably, effects were seen at school even though teachers were unaware of treatment condition and contingencies were not in effect.

Although implemented with an undiagnosed sample, an additional RCT supports BPT. Thompson and colleagues (2009) adapted BPT for preschool children at risk for ADHD by including an increased focus on factors underlying ADHD, including self-regulation and the quality of mother–child interactions. Significant effects of the treatment were found on parent reports of ADHD symptoms and social and behavioral problems compared to a usual community care condition.

Behavioral Classroom Management/Behavioral School Interventions

BCM, like BPT, has been classified as a well-established treatment for ADHD for over fifteen years (Evans et al., 2013; Pelham et al., 1998; Pelham & Fabiano, 2008). As discussed above, early definitive studies of BCM using single-subject experimental methodologies in controlled or specialized classrooms revealed that systematic behavioral contingencies in the form of positive reinforcement (e.g., token economies) and/or prudent negative consequences yield powerful effects on observed behaviors, including on-task behavior and academic productivity while the programs are in effect (Hinshaw et al., 2007). In a recent meta-analysis of sixty studies conducted between 1996 and 2010, school-based interventions, including contingency management as well as academic and self-regulation interventions, were associated with moderate to large improvements in academic and behavioral functioning of students with ADHD (DuPaul et al., 2012). Studies of academic (e.g., peer tutoring, computer-assisted) and self-regulation interventions represent new additions to the evidence base for behavioral interventions since the last review. While promising, these studies are limited to single-subject designs (so are not included in the table); larger sample controlled trials of these intervention approaches are needed.

Since the last review three randomized trials of BCM have been published, all of which are supportive. The first two studies evaluated the efficacy of a Daily Report Card (DRC) for elementary students with ADHD, one in the context of general education (Murray et al., 2008) and one in the context of special education services (Fabiano et al., 2010). The DRC has been used extensively over the years, including as an intervention in several multicomponent studies (Barkley et al., 2000; MTA, 1999; Owens et al., 2005), but had not been systematically evaluated in a large randomized trial. The DRC asks the teacher to rate predetermined specific behaviors targeted for improvement each day; the parent provides rewards at home based on the day's ratings. Murray and

colleagues (2008) used a conjoint behavioral consultation approach to engage parents and teachers in the treatment; Fabiano and colleagues (2010) used separate teacher and parent training meetings. Compared to services as usual, the DRC condition in both studies led to significant improvements in academic skills and productivity (Murray et al., 2008) and teacher ratings of academic productivity, parent and teacher ratings of oppositional defiant disorder and conduct disorder, and blinded observations of classroom behavior (Fabiano et al., 2010).

Mikami and colleagues (2013) compared two methods of managing classroom behavior of elementary school-aged students in an analogue classroom setting. The two treatments both included behavioral contingency management. However, in one of the treatments, MOSAIC, peer inclusion training was added to reduce rejection, social devaluation, and exclusion of children with ADHD. At the end of the two-week program, social behavior problems did not differ between the two groups. However, children (especially boys) with ADHD in the MOSAIC group were less often rejected by their peers and had more reciprocated friendships than those in the standard BCM condition. This study shows that while traditional contingency management improves social behaviors, strategies to increase peer group inclusiveness can provide incremental benefits for peer relationships among youth with ADHD.

Child Skills Training

In contrast to BPT and BCM, which train parents and teachers to deliver the intervention to children, child skills training programs directly train children in skills they then apply themselves. Organizational skills training programs address the substantial difficulties youth with ADHD have in organizing tasks, managing their time, and planning effectively (Langberg et al., 2011, 2008). These skills are particularly important in academic settings since poor organizational skills often translate into problems with classwork and homework completion, test performance, and report card grades, all of which are crucial to academic success (Power et al., 2006; Schultz et al., 2009).

Two programs, one for children (Abikoff et al., 2013) and one for adolescents (Langberg et al., 2012), have recently been evaluated in randomized trials. Both approaches involve training youth in strategies for organizing their belongings (e.g., binders, backpacks, lockers) and tracking assignments using an assignment book. Checklists are used to manage multiple tasks, and incentives are used to reward successful organization. Abikoff and colleagues (2013) compared the Organizational Skills Training intervention delivered directly to children to PATHKO, an intervention that involved training parents and teachers to reinforce children contingently for meeting endpoint target goals and a waitlist control. Organizational Skills Training and PATHKO each involved twenty individual sessions over ten to twelve weeks. Both treatments resulted in robust sustained functional improvements per parent and teacher report of organizational skills as well as family relations relative to the waitlist control group. Organizational Skills Training showed greater effects on a parent-reported measure of organizational skills than PATHKO, but in most ways the two treatments were comparable. Clinically significant effects were notable, with 60% of children in both of the treatment conditions, but only 3% of the control group, no longer meeting inclusion criteria for organizational skills problems,. In contrast to many studies, effects were maintained at follow-up during the subsequent school year.

In a second study, Langberg and colleagues (2012) evaluated the Homework, Organization, and Planning Skills intervention with middle-school students with ADHD. This intervention includes sixteen sessions designed to be implemented by school-based mental health professionals in the school setting. Two parent sessions are also included to encourage parent monitoring and reinforcement of child skills. Children receiving the intervention demonstrated significant improvements relative to a waitlist comparison group on parent ratings of ADHD, organization, planning, and homework completion, although these positive outcomes did not extend to teacher reports. Of note was the fact that school clinicians were able to implement the manualized intervention with fidelity despite no formal ongoing consultation.

Behavioral Multicomponent Interventions

Driven by limited cross-site generalizability of treatment gains, a number of multicomponent behavioral interventions recently have been developed and evaluated. These multicomponent interventions include

a combination of BPT, BCM, and/or child skills training across all age groups from preschool through high school. In addition to directly targeting problems across home and school contexts, these intervention combinations can synergize the effects of the individual components. This may be especially true for child skills training, since it is likely that such skills training will be most beneficial when ongoing monitoring and incentives are provided by parents and/or teachers, since didactic learning alone likely will be insufficient.

The Child Life and Attention Skills (CLAS) program includes home, school, and child skills training components and targets children with the inattentive presentation of ADHD (Pfiffner et al., 2007). The program emphasizes adaptive skills, functional competence, and compensatory strategies; uses cues, prompts, and routines; and involves teachers and parents to provide necessary environmental supports at school and at home. Parents and children attend eight to ten concurrent group meetings and up to five family meetings, and teachers attend up to five consultation meetings with a therapist and each child's family. Children are taught a series of modules focused on independence (homework/study skills, self-care skills, getting chores done, routines, organization, and time tools) and social skills (making friends, handling teasing, assertion, accepting, being a good sport, and problem solving). The parent group acquires strategies to support their children's use of the child skills at home and at school as well as traditional BPT strategies adapted to address impairments of the inattentive presentation. Teacher consultation meetings focus on development and implementation of an individualized daily report card and classroom accommodations specific to the concerns of each child (e.g., additional time or "time challenges" to complete work, preferential seating, reduction in workload, use of assignment book, use of completed work folder). Target behaviors are based on the needs of each child and typically include academic work (e.g., completion of assigned work, completion and return of homework, accuracy of completed work), work behavior/study skills (e.g., following directions, having necessary materials to begin work, getting started on work, staying on task), and social interactions (e.g., entering peer groups, accepting consequences, being a good sport, using assertive behavior). Skills taught in the child group are shared with teachers so that the children's use of these skills can be reinforced (often by including them as targets on the classroom challenge) at school. Parents are taught a set of transferable skills for working with their child's teachers in the future.

The results of an RCT indicate that children who received CLAS had significant improvements in aggregate parent and teacher ratings of ADHD symptoms and severity, as well as social and organizational skills, at posttreatment relative to a community control; these improvements were sustained at three to five months of follow-up (Pfiffner et al., 2007). These results were subsequently replicated and extended in a large-scale, two-site randomized clinical trial of CLAS that revealed significant benefit for the integrated, multicomponent treatment compared to usual care on parent and teacher reports of inattention symptoms and social, organizational, and global impairments; the gains compared to BPT on parent and teacher reports of organizational skills and teacher reports of inattention symptoms and social and global impairment, with evidence of maintenance of treatment effects at five to seven months of follow-up (Pfiffner et al., 2014).

Based on the success of CLAS, Pfiffner and her colleagues extended this program to target all ADHD presentations, with the objective of establishing sustainable implementation in a public school setting (Pfiffner et al., 2011). The adapted intervention, the Collaborative Life Skills program, is designed to be implemented at the child's school by existing school mental health personnel. Findings from a within-subject design reveal broad benefits on attention, academics, organization, social behavior, and classroom engagement (Pfiffner et al., 2013); a randomized trial comparing Collaborative Life Skills to usual school services is under way.

Power and colleagues (2012) expanded the focus of traditional parent training programs by developing the Family-School Success program, a family-mediated educational intervention with BPT and BCM components. Family-School Success includes twelve sessions with six co-occurring parent education and child recreational group sessions, four individualized family therapy sessions, and two family–school consultation sessions including parents and teachers. Standard behavioral parent education strategies were combined with a daily report card, homework interventions, and conjoint behavior consultation. In comparison to a psychoeducation support group, Family-School Success resulted in small to moderate effects on the quality of family–school

relationships, homework performance, and negative/ineffective parenting, even though about 40% of the youth were already taking medication (Power et al., 2012). A version of Family-School Success has been developed for younger elementary students at risk for ADHD, with promising effects on parenting skills and teacher ratings of ADHD and oppositional defiant disorder symptoms and the student–teacher relationship (Mautone et al., 2012).

Multicomponent programs have also been evaluated for preschool and early elementary school. Kern and colleagues (2007) compared a multicomponent, multisetting intervention (including parent education classes and individualized assessment-based intervention in the home and in the preschool or daycare) to parent education alone. Both interventions resulted in comparable and significant improvements in children's behavior and preacademic skills at posttreatment and one year later, although the absence of a no-treatment control group limits understanding of the role of maturation in these changes.

The Incredible Years program (Webster-Stratton et al., 2011) includes BPT, BCM, and child skill training components, which can be implemented separately or combined. This intervention was developed for preschool disruptive behavior problems but was evaluated specifically for four- to six-year olds with ADHD in a recent twenty-week RCT combining only the BPT and child skills training components. Results showed improvements in child inattention, hyperactivity, externalizing behaviors, social competence, and emotion regulation by mother and father reports relative to a waitlist control. Improvement in maternal parenting was also notable per mother self-report and independent observations. Treatment effects were also found at school as seen in teacher-reported externalizing behavior and observations of children's social interactions in the classroom and on tests of social problem solving and feelings literacy.

The First Steps to Success program, also developed for externalizing problems, combines BPT and BCM and was evaluated for children with ADHD in kindergarten through third grades. School personnel implement BPT and BCM in the school, targeting children's externalizing behavior problems. The program consists of thirty days of BCM at school and six home sessions focused on teaching parents BPT strategies. Seeley and colleagues (2009) compared First Steps to a usual care control group and found greater improvement in ADHD behaviors, social skills, and academic problems at school with the First Steps program. However, improvements were not found at home, suggesting that the parent component may not have been sufficient.

Multicomponent treatments also are beginning to emerge at the middle- and high-school level. This is a time when expectations for academic, social, and behavioral independence increase exponentially, and the increased demands are especially challenging for youth with ADHD. Developmental adaptations have been made to programs originally developed for younger youth to better fit the needs of adolescents and to address the changing requirements at school. For example, given their increased cognitive capacity and desire for independence, there is an increased emphasis on teens taking a more active role in their own treatment. Organizational skills interventions are prominently featured in these treatments, given the importance of these skills and notable deficits for ADHD in this area. Meyer and Kelley (2007) evaluated the effectiveness of a one-session training (followed by weekly follow-up phone calls for four weeks) for middle-school youth with ADHD; the training focused on strategies for effective homework completion, monitoring of targeted homework behavior, and general study skills. The effectiveness of self-monitoring versus parent monitoring of homework after the one-session training was compared. Results indicate that both interventions improved parent-rated homework problems and teacher-rated classroom performance, as well as percentage of completed homework, compared to a waitlist control group.

The Challenging Horizons Program (Evans et al., 2011) is a comprehensive school-based treatment program for adolescents with ADHD that combines components for the family and teen and is integrated into the school setting. It incorporates many of the features discussed above. An after-school version has been evaluated in comparison to a community care control condition (Evans et al., 2011). The program consists of three family check-up meetings to motivate and engage families in the treatment. Thereafter, students attend the program for 2.5 hours two days a week, where they receive group interventions for improving social and educational skills. They also receive one-on-one meetings with a counselor to review progress, practice specific skills, and maintain a therapeutic relationship and connection with the program. The counselors work with each student's

parents and teachers to ensure that appropriate problems are being addressed and to facilitate generalization from the after-school program to school and home. Every student uses an assignment notebook for homework, with school and home contingencies for its correct use. Students are also taught note-taking and study skills; they practice these first in the program and then are required to show that they use the skills at school and at home. Outcomes show that students in the Challenging Horizons Program improved relative to those in the control condition on measures of symptoms per parent report and school impairment per teacher report (Evans et al., 2011).

Incremental Effects of Multimodal Combination Treatments

Given the powerful short-term effects of medication and behavioral interventions, yet the limited capacity of either treatment modality to normalize functioning or to substantially alter long-term adverse outcomes, a key question over the years has been whether behavioral interventions can add incremental improvement to medication or vice versa. An underlying assumption has been that the combined treatment might provide optimal effects, since medication and behavioral interventions would each target different domains and medication would allow for sufficient symptom management to allow children to learn adaptive skills taught through behavioral interventions, which they could then apply across time and settings to improve generalization.

The largest study to have evaluated the separate and combined effects of psychosocial and medication treatments continues to be the Multisite Treatment Study for ADHD (MTA), conducted in the 1990s; follow-up of participants has occurred at regular intervals since then. As reviewed in the previous version of the chapter, 579 children aged seven to 9.9 years were randomly assigned to (a) medication management, (b) intensive behavioral treatment (BI, combining BPT, BCM, and an intensive summer treatment program), (c) combined behavioral and medication treatment, or (d) community comparison. The behavioral treatment included thirty-five BPT sessions for parents, both group and individual; therapist-facilitated consultation and coordination with the children's teachers; an eight-week summer treatment program; and paraprofessional aide involvement in the classroom for three months following the summer treatment program. These treatments were faded toward the end of the fourteen-month intervention period.

Of particular relevance to the topic of this chapter, initial published findings revealed that BI produced gains in ADHD symptoms, comorbid symptoms, and school, family, and peer-related impairments similar to community care (most of whom were taking medication); the benefits of BI on ADHD and oppositional defiant disorder symptom reduction were smaller than those from medication; and measures showing gains from BI were based on parent and teacher ratings rather than objective measures. Since then, several secondary studies have shown stronger effects for BI: Composite measures of parent and teacher rating scales show superiority of BI over community care and incremental benefit from combined treatment over medication alone. Most recently, Langberg and colleagues (2010) showed main effects for BI on parent ratings of homework problems; only those who received BI demonstrated sustained improvement (ten months after treatment ended) in homework problems in comparison to routine community care. Unique benefits of BI were also found on an objective measure of observed parenting skill during a clinic-based parent–child interaction (Wells et al., 2006). Outcomes from other objective assessments, including peer sociometric indicators and blinded classroom observations, have failed to show clear benefit from BI.

Since the last review, thirty-six-month and eight-year follow-up data have been published. At thirty-six months, reports of substance abuse were lower for both behavioral treatment groups compared to medication only and the community control (Molina et al., 2007). No group differences have been reported on any other measures of symptoms and impairments at either of these time points.

Two additional randomized trials of medication and BI have been published since the last review. A study by Van Den Hoofdakker and colleagues (2007) evaluated BPT as an adjunct to routine clinical care in the form of family support and medication as needed. They found that BPT enhanced the effectiveness of routine clinical care in reducing behavioral and internalizing problems and in reducing prescriptions for polypharmaceutical treatment. In contrast, Van de Oord and colleagues (2007) failed to find an additive effect of ten-week multimodal behavioral treatment to optimally dosed stimulant treatment on parent and teacher reported ADHD

symptoms and social skills, parenting stress, or child self-report of self-worth and anxiety. These latter findings are in concert with earlier studies that failed to find incremental effects of BI with optimally dosed youth (e.g., Abikoff et al., 2004; Hechtman et al., 2004).

These inconsistencies within and across studies highlight the difficulty of evaluating the comparative and incremental effects of BI and medication. The findings reveal that these treatments may indeed differ in their relative effects on different outcome measures. Also, inconsistent findings may be the result of differences in the relative intensities of BI and medication across studies. Evidence for this comes from studies that have been carried in the context of a summer treatment program that allowed for careful standardization and control of varying intensities or doses of BI and medication. Treatments were evaluated in a classroom setting (Fabiano et al., 2007) and replicated in a social-recreational setting (Pelham et al., 2014). Multiple doses of behavior modification (none or low and high intensity) were crossed with medication (placebo, 0.15, 0.3, 0.6 mg/kg methyphenidate). The intensity of behavior modification was varied according to how various aspects of standard BCM were applied (use of rules, point system, DRC, time-out, social reinforcement, rewards), with the high intensity representing the most consistent and contingent application of these systems and the low intensity representing a less consistent and contingent application that was more similar to a regular classroom or recreational setting; the no behavior modification condition did not implement these systems. Results indicated that incremental effects of combined treatments occurred at the low doses of treatment, with increasing dose of either resulting in more modest improvement. There were no benefits of combined treatments when the dosage of either treatment was high. In addition, low-dose behavior modification combined with a low dose of medication was equivalent to a high dose of medication or high behavior modification used alone. These results clearly demonstrate that questions about relative efficacy and incremental effects need to take into account the dose or intensity of each treatment.

Moderators and Mediators of Treatment Outcome

A number of factors have been found to moderate the impact of BPT, in part due to barriers to treatment engagement and attrition (Lundahl, Risser, & Lovejoy, 2006). Moderators include low income, parent education level, single-parent families, a lack of father involvement, high parent stress, and a lack of parent social support; all predict less favorable outcomes (Chronis et al., 2004; Harwood & Eyberg, 2006; Pelham & Fabiano, 2008). In addition, severe marital discord, parent psychopathology (e.g., depression, ADHD, antisocial behavior), and parental drug abuse or dependence all can reduce the efficacy of parent training (Chronis et al., 2004). Moreover, positive parental expectations before and throughout treatment have been found to predict better treatment engagement in BPT and better child outcomes (Kaiser et al., 2010), and including a child component can reduce premature termination in BPT (Miller & Prinz, 1990), suggesting that including the child in treatment may exert a positive effect on parents' motivation for treatment. Practical aspects, such as program times, locations, activities, and advertised benefits of the treatment, also influence utilization of BPT programs (Cunningham et al., 2008).

Child factors also predict response to parent training. The severity and nature of symptoms and problems are likely the strongest predictors of whether or not (or to what degree) treatment produces desired change. For example, Langberg and colleagues (2010) found that, at the twenty-four-month follow-up in the MTA study, the benefits of the combined intervention on homework problems were strongest for children with moderate parent-rated ADHD symptoms.

Few studies have examined specific mediators and moderators of BCM, but as with BPT, it is likely that implementation factors such as engagement and fidelity are important. For example, although evidence supports the utility of specific interventions, such as DRC, recent studies show that practical considerations such as holding conjoint parent–teacher consultation meetings at the child's school (Murray, Rabiner, Schulte, & Newitt, 2008) and allotting leave time for teachers so that they can attend consultation meetings are important (Owens et al., 2008). The use of existing school infrastructure for engaging teachers and implementing the treatment may result in more sustainable implementation of interventions (Atkins et al., 2008).

Although not evaluated for ADHD per se, a variety of process factors associated with implementation of behavioral treatments also can affect outcome. As with any intervention, the therapist–client relationship influences outcome in behavior therapy

(Webster-Stratton & Herbert, 1993). Therapist warmth, knowledge of social learning principles and disruptive behavior disorders, likeability, and communication skills all are likely to contribute to more positive outcomes. Helpful therapist behaviors include active listening skills to guide and maintain parents' responses to open-ended questions, whereas overly supportive statements early in therapy may reinforce feelings of client helplessness, which might contribute to dropout (Harwood & Eyberg, 2006). Active parental engagement and compliance with treatment, as measured by parental adherence to between-session assignments (e.g., the extent to which they implement the strategies they are taught) and to a lesser extent attendance at sessions, are important predictors of child outcomes (Clarke et al., 2013). Compliance with treatment can be enhanced using motivational strategies (Dishion et al., 2003; Nock & Kazdin, 2005) and specific prompts (e.g., reminder phone calls between sessions that prompt parents to complete homework or to come to the next session).

Finally, studies have evaluated mechanisms underlying effects of treatment and report that improved child outcomes appear to be a function of the degree of change in the areas directly targeted in the treatment. For example, for parent-mediated interventions, changes in parenting predict child outcomes. In the MTA study, the combination treatment, when associated with improved parenting, was prone to yield not just improvement in behavior but also normalization of such behavior (Hinshaw et al., 2000). In a separate study of BPT, improvement in child behavior was mediated by change in observed maternal negative parenting (Chronis-Tuscano et al., 2011). In child-focused intervention, the degree of change would be expected to relate to the extent to which the child used the organizational skills taught. Indeed, Langberg and colleagues (2013) found that adoption of the binder materials organization system predicted parent-rated improvements in organization, planning, and homework problems and demonstrated the benefit of teaching students with ADHD to use a structured binder organization system for organizing and transferring work to and from school.

Cognitive Training/Neurofeedback

In recent years, treatment efforts have been directed to modify neurocognitive deficits, which are thought to underlie many of the core symptoms and impairments of children with ADHD. Computer-based training exercises with extensive practice and feedback have been employed to facilitate development of hypothesized areas of executive function and attention deficiencies. Improvement in these underlying processes has been posited to transfer to improvements in other tasks and activities relying on these processes, such as academic functioning. Several randomized trials have evaluated one such program, Cogmed Working Memory Training (CWMT). CWMT is a computer-mediated program with a gamelike interface that requires children to complete working memory tasks, with the difficulty level of the working memory demands adjusted based on performance after each trial. Children complete these tasks for approximately twenty-five to forty-five minutes daily for four to six weeks. Although trials have generally found improvements on trained working memory tasks (resembling tasks in CWMT) and to a lesser extent on nontrained cognitive tasks (which rely on the same cognitive processes) relative to a waitlist control (Beck et al., 2010), a placebo control (Chacko et al., 2013; Green et al., 2012; Klingberg et al., 2005), or an active treatment comparison (Gray et al., 2012), effects on ADHD symptoms and day-to-day impairments have been minimal. Although several studies reported some improvements in parent ratings of ADHD symptoms (Beck et al., 2010; Klingberg et al., 2005), effects on blinded teacher ratings or academic functioning/achievement have not been found. In the most methodologically rigorous evaluation of CWMT, in which concerns from previous studies of CWMT about the equivalence of the placebo version were addressed, no differences were found on any outcome measure other than improvement on verbal and nonverbal working memory storage (Chacko et al., 2013). Thus, while CWMT can improve certain aspects of working memory, there is no evidence that it can affect any other domains of functioning.

Other cognitive training programs aim to improve selective and sustained attention (Hagan et al., 2008; Kerns et al., 1999; Semrud-Clikeman et al., 1999; Shalev et al., 2007). These attention training programs also use computer-mediated tasks and follow a similar training regimen as that described for CWMT (Hagan et al., 2008; Shalev et al., 2007). Evidence for treatment effects on daily functioning is limited. In a recent meta-analysis of twenty-five

studies of cognitive training, Rapport and colleagues (2013) reported some preliminary evidence for improvement on trained tasks measuring short-term memory (medium effect size) and unblinded raters' assessment of ADHD symptoms (parents) but scant evidence of any transfer to unblinded ratings of symptoms and daily functioning at home or school or on tests of academic functioning.

Neurofeedback has been used to alter brainwave patterns posited to underlie ADHD and has been evaluated as a potential treatment for children with ADHD (Lofthouse et al., 2011; Sherlin et al., 2010). Children with ADHD have been found to have low levels of arousal in frontal areas of the brain as a result of excessive theta (slow) waves and a deficit of beta (fast) waves. Children are taught how to control their brain activity patterns through auditory and visual feedback on changes in the brain's electrical activity measured by scalp electrodes. Through intensive neurofeedback training (approximately thirty to forty hours over two to three months), the goal is to teach children through operant and classical conditioning to increase beta and decrease theta brain wave patterns in frontal areas. Several studies have reported evidence that this treatment can improve beta–theta activity as well as symptoms of ADHD per blinded parent and teacher report (Bakhshayesh et al., 2011; Gevensleben et al., 2009, 2010), but effects on measures of social, academic, and home functioning have not been found. However, methodological concerns persist (lack of adequate blinding of study participants, raters, and neurofeedback raters; no studies with appropriate placebo treatments, such as sham-neurofeedback, that simulate the nonspecific effects of neurofeedback; and failure to track concomitant treatment [Lofthouse et al., 2012]), which limit the conclusions that can be made about overall effectiveness.

Cultural Factors

The behavioral treatments described in this chapter have been developed and tested with predominately English-speaking European American samples; thus, the extent to which these treatments and treatment outcomes generalize to diverse samples is not clear. Very few behavioral clinical trials included adequate numbers from diverse populations to investigate differential treatment outcomes among groups. One exception can be found in secondary analyses from the MTA study by Jones and colleagues (2010), which compared behavioral treatment effects for African American, Latino, and Caucasian children. Results suggested that all three groups responded comparably, providing initial promise regarding the universality of behavioral interventions (Jones et al., 2010). However, the MTA study excluded participants without English proficiency, limiting generalization to this likely less acculturated population, and sample sizes for other ethnic minority groups, such as Asian or American Indian families, were insufficient for separate analyses.

Current guidelines for evidence-based treatment with ethnic minority youth call for the examination of culturally modified treatments (for full reviews, see Huey & Polo, 2008; Miranda et al., 2005). Although several culturally modified treatments for children have been developed with positive results (e.g., PCIT for Mexican Americans by McCabe & Yeh [2009]), no trials investigating culturally modified ADHD treatments have been reported to date. It may be especially important to examine the impact of culture and ethnicity on behavioral treatments, as these interventions focus on modifying the social environment (e.g., parenting practices), which can be highly influenced by culture (Weis & Toolis, 2010). Crucially, despite the fact that ethnic minority children display comparable rates of ADHD, they are far less likely to receive ADHD services and participate in research compared to nonminority youth (Alegría et al., 2007; Eiraldi et al., 2006; Faraone et al., 2003; National Institutes of Health, 2002; Willcutt, 2012). Culturally modified recruitment strategies may be necessary to ensure adequate representation of ethnic minority populations (e.g., Haack et al., 2012, in press; Ojeda et al., 2011). Also, culturally appropriate assessment measures validated with the specific population of interest may be needed (Haack & Gerdes, 2011; Lee & Humphreys, 2011). For example, the ADHD-FX (Haack et al., in press), which was developed specifically for use with Latino families, emphasizes functional impairment related to academic, social, and family functioning, since these constructs are thought to be less culturally biased than ADHD symptomatology (Gerdes et al., 2013; Rothe, 2005).

SUMMARY OF FINDINGS

The evidence base for behavioral interventions has continued to expand in recent years, broadening both

the impact and scope of these interventions, as summarized in the points below.

1. Several type 1 studies, which have the highest level of scientific rigor, show strong, positive effects of BPT, BCM, and behavioral multicomponent interventions. Effects are seen on parent and teacher reports of ADHD symptoms, key areas of impairment including social competence and acceptance, and academic productivity as well as on blinded observations of classroom behaviors and parent–child interactions. Many more type 2 RCTs also show statistically and clinical significant positive effects of BPT, BCM, childhood skills teaching, and multicomponent behavioral interventions on parent and teacher ratings of symptoms, social and academic functioning, and parent–child relationships compared to no treatment and active treatment controls. Together these studies confirm the status of behavioral interventions as well-established treatments for ADHD.
2. Adaptations of BPT have been developed to address barriers and reach new populations. Programs specifically designed for fathers, single mothers, and depressed mothers all report benefits relative to no-treatment controls. Although child outcomes from these adapted models are not always superior to traditional BPT (e.g., Fabiano et al., 2009a), the adapted treatments do appear to increase parent engagement and treatment satisfaction, and gains from these adapted treatments have been maintained in follow-up assessments up to one year later. Telephone-mediated delivery also shows initial efficacy and holds promise for addressing travel barriers.
3. Novel organizational skills training programs for children show positive effects for ameliorating the common and impairing organizational deficits that typically accompany ADHD symptoms. This form of treatment has the potential to improve treatment generalization since youth can apply these skills across settings and there is less reliance on parents and teachers to consistently support the youth's efforts through special contingencies. There is some suggestion that the assumptions of greater generalizability may hold (e.g., Abikoff et al., 2013; Meyer & Kelley, 2007), and at least one study showed normalization of organizational skills in 60% of cases (Abikoff et al., 2013). Studies of academic interventions and self-regulation are also promising but have yet to be evaluated in a large-scale randomized trial.
4. There is greater use of cross-setting and multiple component behavioral treatments that infuse treatment throughout the day to address longstanding concerns about a lack of generalization and maintenance of treatment gains. These studies show superior outcome to no treatment or usual care controls and, more importantly, are showing improved maintenance of treatment gains (often into the next school year) and overall greater cross-setting effects than single-setting treatments (Abikoff et al., 2013; Pfiffner et al., 2014; Webster-Stratton et al., 2011). Recent efforts focused on promoting effective school–home partnerships have yielded benefits for family–teacher relationships as well as student outcomes even among families of medicated children (Power et al., 2012).
5. The previous (2007) review reported that BI, on average, was less effective than medication and that the jury was still out as to whether combination treatments were superior to medication alone. Since then, it has become increasingly clear that comparisons of medication and BI are complex and difficult; there is a need to take into account a number of factors, including the outcome being measured and the dose of the intervention. When this is accomplished, combined multimodal treatments appear to reduce the needed dose or intensity of each intervention. In addition, existing medication treatments appear to have greatest impact on symptom reduction, while behavioral treatments may have greatest impact on some areas of impairment (e.g., parenting, homework success), consistent with the respective targets of these two treatment modalities.
6. There has been an increase in research on treatments for adolescents and preschool children showing that BI, with developmentally appropriate adaptations, can be effective with these age groups.
7. There have been a number of efforts to develop alternative nonpharmacologic treatments,

including cognitive training and neurofeedback. Although existing cognitive training programs have not been found to be efficacious, there is some preliminary evidence to support neurofeedback, but further study is needed before clinical application can be recommended.

3. While some studies have shown evidence of maintenance of gains, the time period assessed is relatively short (months rather than years) (Abikoff et al., 2013, Pfiffner et al., 2007). As a consequence, ongoing or at least periodic treatment, especially during periods of developmental transition, may be necessary.

LIMITATIONS AND QUALIFICATIONS

A number of limitations and qualifications need to be considered.

1. Although several additional type 1 outcome studies of BI have been reported, there are still relatively few of these in comparison to the number of type 1 studies of medication, mostly because there has been limited use of objective or blinded measures. As a result, a good deal of the evidence supporting the use of BI remains based on reports from parents and teachers who were involved with the treatment. Clearly, there is a need for documentation of BI effects using nonbiased measures of outcome, especially outcomes related to real-world indices of successful functioning (e.g., report card grades, academic achievement, sociometric ratings).
2. The size of treatment effects, while large, is usually below full normalization. Often, this is a function of the extent to which parents and teachers can implement the treatment recommendations with fidelity (e.g., Clarke et al., 2013). It is notable that the one study with high rates of normalization (60%) was conducted with a relatively high-functioning population (Abikoff et al., 2013). In addition, treatment effects are less prominent on sociometric measures, although a recent trial shows effects on teacher perceptions of peer acceptance from teachers blinded to the intervention (Mikami et al., 2013). Also, behavioral treatments have had little impact on academic achievement, although they have had very strong positive effects on academic productivity and homework performance. Gains in achievement may require longer-term treatment and/or greater focus on academic skill building.

FUTURE DIRECTIONS

Findings from this review, coupled with those of the previous review, provide strong support for the efficacy of BI for ADHD. The next generation of studies would do well to address the above limitations and discover how we can maximize effects and tailor current clinical approaches to best meet the needs of varied children, families, and circumstances.

1. Larger-scale trials are needed to evaluate mechanisms of change and moderators of effects to better tailor existing interventions and to develop innovative approaches to treat those who may not be responding as well. Successful tailoring of interventions will also require evaluations of optimal dosing, combinations, and sequencing of various behavioral treatment components as well as behavioral and medication treatments for individual children and families. In addition, closer links between advances in basic science delineating the underlying mechanisms of the disorder and clinical science on intervention development may identify more targeted treatments.
2. There is a pressing need to improve the accessibility of empirically supported behavioral treatments to broad, high-risk populations. The vast majority of RCTs included in this review have been conducted in university-based clinic settings with highly trained clinicians. However, these interventions are seldom implemented in other settings, such as schools or community clinics, and are therefore not available to many of those in greatest need. The extent to which these interventions can be directly exported to the community is not known, although recent efforts suggest that with some relatively minor modifications and focused training for providers, this should be possible (Pfiffner et al.,

2013). Issues of cost-effectiveness are critical for successful translation and dissemination into community settings. Interventions need to be feasible and acceptable, as do the training requirements for those who deliver the interventions (e.g., clinicians, teachers). To this end, innovative approaches may include greater use of existing community resources and emerging technologies (e.g., interactive Web-based treatment and training). Also, culturally modified treatment programs may be necessary to encourage participation, engagement, and optimal treatment outcomes across diverse ethnicities and cultures.

3. Greater attention to issues of engagement, adherence, and implementation fidelity on the part of all treatment participants (e.g., teachers, parents, and students) is critical given the association between these factors and treatment outcome (e.g., Clarke et al., 2013; Langberg et al., 2013; Villodas et al., 2013). Targeted treatments to optimize these factors are needed. These efforts also may be facilitated by recent and ongoing technological advances (e.g., use of smartphones for monitoring or implementing behavioral strategies).
4. Long-term outcomes after behavioral interventions have been discontinued have been disappointing (Molina et al., 2007) but are consistent with a chronic disease model of ADHD. Treatment approaches for sustaining effects and addressing new problems that are expected to arise during key developmental transitions (e.g., transition to middle and high school) are needed.
5. Finally, policy research on the ways in which behavioral treatments can best be provided and financed within systems of care (e.g., schools, public and private insurance, community agencies) is sorely needed so that these services become more accessible to all youth and families in need.

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4

Pharmacological Treatments for Attention-Deficit/Hyperactivity Disorder and Disruptive Behavior Disorders

Erica Kass
Jonathan E. Posner
Laurence L. Greenhill

More than 225 placebo-controlled type 1 investigations demonstrate that psychostimulants are highly effective in reducing core symptoms of attention-deficit/hyperactivity disorder (ADHD) in children and adults. In contrast, there are limited type I studies demonstrating that psychopharmacological management with U.S. Food & Drug Administration (FDA)-approved agents for ADHD (stimulants and nonstimulants), atypical antipsychotics, and mood stabilizers decrease the defiant and aggressive behavior characteristic of disruptive behavior disorders, including conduct disorder (CD) and oppositional defiant disorder (ODD). Stimulant treatment evidence has been supplemented by two large multisite randomized controlled trials (RCTs)—the Multimodal Treatment Study of ADHD (MTA Study) and the Preschool ADHD Treatment Study (PATS). RCTs from the past 15 years continue to report several key adverse events associated with stimulants—insomnia, decreased appetite, stomachache, and headache—but have not supported rarer and more serious problems, such as cardiovascular accidents or sudden unexpected death, which were reported in 2006 in the FDA's Adverse Event Report System. Although psychostimulants have been shown to retain their efficacy for as long as 14 months, their long-term academic and social benefits are not as robust. Nonstimulant agents for which there is more limited evidence of efficacy include atomoxetine (ATX), α-agonists, modafinil, and bupropion.

INTRODUCTION

Stimulant medications have become first-line agents for treating ADHD, a major public health problem in the United States. The American Psychiatric Association states in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) that 5% of children have ADHD. The percentage of U.S. school-aged children with a parent report of current medication treatment for ADHD increased from 4.8% in 2007 to 6.1% in 2011. Among those children reported as currently having a diagnosis of ADHD, 69% were taking medication. (Visser et al., 2014). Although the use of ADHD medications is generally lower in European countries than in the United States, the same trend with increased number of prescriptions has been documented in the Netherlands, Denmark, and Spain (Hodgkins, Sasane, & Meijer, 2011; Pottegard, Bjerregaard, Glintborg,

Hallas, & Moreno, 2012; Treceno et al., 2012). A population-based study in Denmark revealed that the percentage of children and adolescents with ADHD being treated with one or more ADHD medications (61%) was similar to the percentage being treated in the United States (69%) (Dalsgaard et al., 2013).

Stimulants ameliorate core ADHD symptoms by reducing excessive gross motor activity, decreasing off-task behavior, increasing compliance with adult requests, and decreasing aggression (Greenhill, Halperin, & Abikoff, 1999). Not only are they effective, but they also have a rapid onset of action and a low rate of adverse events, with only 4% of children having to change to another medication in a controlled study of adverse events (Barkley et al., 1990). This rapid and robust response explains, to some degree, why published treatment research on childhood ADHD in the past four decades has focused on stimulants (Vitiello & Jensen, 1995). Academic researchers have relied on either methylphenidate (MPH) or the amphetamines to study response patterns, adverse events, "normalization" during drug treatment, and patient characteristics among nonresponders.

This chapter updates previous reviews of the ADHD medication treatments that work. As with other chapters in this volume, the study classification system based on published evidence will be used to guide the reader, as shown below. This chapter will include (a) a brief historical perspective on ADHD drug treatment studies, using type 5 reviews to highlight conceptual notions driving drug research; (b) an updated description of current psychopharmacological treatments of choice, supported by recently published type 1 RCTs; (c) a perspective on controversies surrounding the safety of ADHD psychopharmacological interventions; and (d) an updated review of current psychopharmacological treatments of choice for children and adolescents with ODD and CD and aggression (sometimes grouped together with ADHD as the "disruptive behavior disorders"). This final section is an addition to the fourth edition of *Treatments That Work*. In a variety of studies done over the past two decades, the prevalence of children diagnosed with ADHD and either ODD or CD has been shown to range from 45% to 85%, averaging about 55% across studies (Barkely, 2006; Pliszka, 2009), making ODD and CD the most common comorbidities associated with ADHD. Notably, children, especially boys, exhibiting both ADHD and aggressive CD appear to be at the highest risk for poor longitudinal outcomes (Mannuzza et al., 1993).

PREVALENCE OF STIMULANT MEDICATION USE IN THE UNITED STATES

Psychostimulant use has increased fivefold since 1989, and this has raised concern at the U.S. Drug Enforcement Administration—which regulates production—about the risk of abuse and diversion. Production of MPH has tripled over a 10-year period, and 90% of U.S.-produced MPH is used in the United States. Increased MPH use could mean increases in ADHD prevalence, a change in the ADHD diagnosis, improved recognition of ADHD by physicians, broadened indications for use, or an increase in drug diversion and prescription for profit or abuse (Goldman et al., 1998). Analysis of managed-care datasets revealed a 2.5-fold increase in prescribing in the 1990–1995 time period, accounted for by longer durations of treatment, inclusion of girls and patients with predominantly inattention subtype, and treatment of high school students (Safer et al., 1996). An epidemiologically based survey in four different communities found that only one eighth of diagnosed ADHD children received adequate stimulant treatment (Jensen et al., 1999b); another survey in rural North Carolina found many school-age children taking stimulants did not meet *DSM-IV* criteria for ADHD (Angold et al., 2000).

According to a study conducted by the National Institute of Health (NIH) and the Agency for Healthcare Research and Quality, the rate of stimulant prescriptions rose slowly but steadily among children under age 19 from 1996 to 2008. Specifically, the rate went from 2.4% in 1996 to 3.5% in 2008. This corresponded to an average growth rate increase of 3.4% per year, substantially less than the growth rate between 1987 and 1996, which averaged about 17% per year. Overall, prescription use among 6-to 12-year-olds was highest, going from 4.2% in 1996 to 5.1% in 2008, but the fastest growth occurred among 13- to 18-year-olds, going from 2.3% in 1996 to 4.9% in 2008. A hypothesis explaining this increase among adolescents may reflect the recent recognition that as children age they do not always grow out of their symptoms (Zuvekas & Vitello, 2012). Prescription use among preschoolers has remained very low at 0.1% from 2004 onward, and this is the only age group with decreased use between 2002 and 2008.

However, more recent U.S. studies of community samples and Centers for Disease Control & Prevention (CDC)-sponsored epidemiologic data

estimate that prevalence rates of ADHD are higher than what is reflected by rates of stimulant prescriptions. Analysis of insurance claims data have documented steady increases in the prevalence of ambulatory visits for ADHD diagnoses between 2001 and 2010 (Garfield et al., 2012; Getahun et al., 2013). The National Comorbidity Survey, a national face-to-face survey of 10,123 children aged 13 to 17 years in the continental United States, suggested that the lifetime prevalence of ADHD among adolescents was 8.7% (Merikangas et al., 2010). The National Health Interview Survey is a large-scale survey of U.S school-aged children (4 to 17 years) that asks parents about clinician-diagnosed illnesses. Parents' reports of a history of ADHD increased from 7.8% in 2003 to 11% in 2011 (approximately 6.4 million children). This represents an increase of 42% in less than a decade. Among those with a history of an ADHD diagnosis, 83% were reported as currently having ADHD (8.8%) (Visser et al., 2014).

Treatment of adults with ADHD has been the fastest area of increase in the use of stimulant medications. Analysis of data from the 1994 to 2009 National Ambulatory Medical Care Survey (number of visits: 372,702) examined the percentage of adult visits (those 18 years and older) in which stimulants were prescribed. Between 1994 and 2009, there was a substantial increase in stimulant prescriptions during adult outpatient visits, especially for younger adults. Namely, the percentage of visits in which stimulants were prescribed increased from 0.11% (1994 to 1997) to 0.70% (2006 to 2009). Among adults aged 18 to 29 years, the corresponding increase in stimulant visits went from 0.17% to 1.83% (Olfson et al., 2013).

DIAGNOSIS OF ADHD

Treatment with stimulants is indicated when there is a diagnosis of ADHD. However, the ADHD diagnosis has been controversial because there are no confirmatory laboratory tests. The diagnosis is further complicated because the criteria have been revised five times over the past thirty years. The most recent criteria appear in the *DSM*-5 (APA, 2013). ADHD covers two symptom domains (inattention and hyperactivity-impulsivity) and is subdivided into predominantly inattentive, predominantly hyperactive-impulsive, and combined subtypes (APA, 2013).

Guidelines for making the ADHD diagnosis in the office practice context have been published by the American Academy of Pediatrics (2011) and the American Academy of Child and Adolescent Psychiatry (AACAP, 2007). Because ADHD is so prevalent, the AACAP recommends that screening for ADHD should be part of any patient's mental health assessment. This can be accomplished by asking questions about inattention, impulsivity, and hyperactivity, and whether such symptoms cause impairment. In addition, prior to interviewing the patient, the clinician may find it helpful to ask parents and teachers to fill out rating scales containing *DSM-5* symptoms of ADHD. Useful rating scales include the Vanderbilt ADHD Diagnostic Parent Scale (VADPRS), the Vanderbilt ADHD Diagnostic Teacher Rating Scale (VADTRS), the Conners' Parent Rating Scale-Revised, the Conners' Teacher Rating Scale-Revised, and the Swanson, Nolan, and Pelham Rating Scale, Version IV (SNAP-IV). A positive screen on a rating scale, however, does not make a definitive diagnosis of ADHD.

The diagnosis of ADHD must be established by history taken from multiple informants, including the child, the parents, and the teacher. The clinician should address each of the five major *DSM-5* criteria, including age of onset (before age twelve), requirement for impairment in a minimum of two settings, six-month duration of symptoms, and a differential diagnosis ruling out other diagnostic conditions that can cause a patient to experience inattention, hyperactivity, or impulsivity. The confirmation depends on specific symptom criteria encompassing the type, duration, severity, and frequency of ADHD problems. A comorbid diagnosis of autism spectrum disorder is no longer exclusionary of an ADHD diagnosis. The patient must experience at least six out of nine ADHD symptoms in either or both inattention and hyperactivity-impulsivity symptom lists, giving positive endorsement only if the symptom occurs often (at least half of the time). The symptoms must start in childhood, prior to age twelve, and have a chronic course.

A physical examination and medical history should be carried out during the diagnostic evaluation. If the medical examination and history are unremarkable, no additional laboratory or neurological testing is required (AACAP, 2007). Similarly, no routine psychological testing is needed for the diagnosis of ADHD, but it should be performed if "the

patient's history suggests low general cognitive ability or low achievement in language or mathematics relative to the patient's intellectual ability," beyond that accounted for by the ADHD symptoms themselves (AACAP, 2007).

The next diagnostic procedure includes an interview of the child or adolescent to determine whether other psychiatric disorders are present that account for the impairment. Whereas it is helpful to interview a preschool or school-age child with the parent present, older children and adolescents should be interviewed alone because they are more likely to discuss symptoms of substance use, suicidal ideation or behavior, or depression with the parent absent. Because ADHD behaviors in youth are often attenuated during the first few visits with a clinician, direct observations of the child's behaviors in the office cannot be used to confirm or deny the diagnosis of ADHD.

Since a majority of children with ADHD also suffer from at least one other Axis I psychiatric disorder (Biederman et al., 1991), the clinician should ask about symptoms of ODD, CD, depression, anxiety disorders, tic disorders, substance use disorders, ASD, and mania. Symptoms of these disorders are captured by parent symptom checklists (e.g., Achenbach Child Behavior Check List) and rating scales (e.g., SNAP-IV). In addition, the clinician should obtain information about the family history and the patient's prenatal history, developmental milestones, and medical history.

HISTORICAL PERSPECTIVE

In 1937, Bradley, looking for a new treatment for headaches, serendipitously observed that disturbed children and adolescents responded to Benzedrine, a racemic form of amphetamine. This treatment had a dramatic calming effect, while simultaneously producing an increase in academic productivity and a "zest for work." Bradley published other type 6 studies reporting the improvement of children during amphetamine treatment (Bradley, 1937; Bradley & Bowen, 1941). The earliest investigations of these drugs suggested that psychostimulants operated by stabilizing cortical circuits, as shown by their ability to increase the seizure threshold (Laufer, Denhoff, & Solomon, 1957). These medications also decreased oppositional behavior in boys with CD attending a residential school (Eisenberg et al., 1961) and reliably reduced the target symptoms of ADHD as measured by parents and teachers (Conners, Eisenberg, & Barcai, 1967). However, these early protocols lacked uniform diagnostic criteria, reliability measures, and multiple observers, so they must be judged type 2 studies. Since then, more carefully designed, placebo-controlled studies have demonstrated that both amphetamine- and MPH-based compounds produce statistically significant and clinically meaningful reductions in ADHD symptoms within one hour of taking an effective dose. Starting in 1977 (Barkley, 1977), a series of type 5 literature reviews summarized these studies. Wilens and Biederman's (1992) MEDLINE search retrieved more than 990 psychostimulant treatment studies published between 1982 and 1991. Further verification appeared in a type 4 meta-analysis (Swanson, 1993) that analyzed the reviews, concluding that the most marked effects of stimulants can be observed on teacher measures of classroom behavior (with effect sizes ranging from 0.63 to 0.85) and that lesser effect sizes (in the range of 0.19 to 0.47) can be identified on measures of intelligence or academic achievement. The effect sizes observed on teacher ratings would satisfy rigorous phase III, premarketing, investigational new drug applications to the FDA.

The psychostimulants MPH and dextroamphetamine (DEX) produced significant reductions in task-irrelevant activity and classroom disturbance (Barkley, 1977; Jacobvitz, Sroufe, Stewart, & Leffert, 1990), with robust responses occurring in 65% to 75% of the 4,777 ADHD subjects treated (Wilens & Biederman, 1992). This review included 4 preschool, 96 school-age, 6 adolescent, and 6 adult controlled studies. More recent type 4 meta-analyses verified these findings and included "A Review of Therapies for Attention Deficit Hyperactivity Disorder" by the Canadian Coordinating Office for Health Technology Assessment (Pelham, Hoffman, Lock, & SUNY CONCERTA Study Group, 2000), "The Treatment of Attention Deficit Hyperactivity Disorder: An Evidence Report," contracted to the McMaster University Evidence-Based Practice Center by the Agency for Health Care Research and Quality (1998), and others (Campbell & Ewing, 1990; Leech, Richardson, Goldschmidt, & Day, 1999).

The large type 5 reviews touch on diverse types of responses to stimulants, including the best methods of determining the optimal stimulant dose to reduce ADHD behaviors (Barkley, 1977, 1982; DuPaul &

Barkley, 1990), the mechanisms of action (Solanto, 1984), whether stimulant response is diagnostically specific (Gittelman, 1980), and the ability of these medications to enhance other therapies (Gittelman, 1987). In addition, dosing methods, paradoxical stimulant effects, and whether stimulants improve academic performance (DuPaul & Barkley, 1990; Jacobvitz et al., 1990) are addressed.

Dosing methods and dose-response issues were considered in the seminal paper by Sprague and Sleator (1977), which reported dissociation of cognitive and behavioral MPH responses in ADHD children. Using weight-adjusted doses, they found that children responded optimally to a memory task at a low dose (0.3 mg/kg) but required higher doses (1.0 mg/kg) to attain optimal behavioral control in the classroom. This paper established the customary weight-adjusted MPH dosing standard that would permeate the ADHD drug-treatment literature until the present and also raised the question whether MPH doses optimized for behavior might not be best for learning.

Reviews of pre-1990 drug studies (Jacobvitz et al., 1990; Wilens & Biederman, 1992) concluded that there was no diagnostically specific positive response to stimulants for ADHD children. No differences in response were found between stimulant-treated ADHD children, stimulant-treated normal children, or clinically referred non-ADHD children (Rapport et al., 1980). Also rejected was the notion that ADHD children show a "paradoxical" slowdown response to stimulants. Rather, the literature shows a decrease in aimless activity, an increase in attention, and an elevation in heart rate and blood pressure in all groups of children, regardless of diagnosis.

These reviews also grappled with the question of whether stimulants, so successful in short-term trials, lead to long-term improvements. ADHD follow-up studies (Barkley, Fischer, Edelbrock, & Smallish, 1990; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993; Weiss & Hechtman, 1993) have demonstrated that ADHD core symptoms continue into late adolescence and even into adult life. No stimulant benefit has been shown to persist when children are treated over the years, as indicated in the 2-year posttreatment follow-up reports of the National Institute of Mental Health (NIMH) MTA Study (Jensen, Arnold, Severe, Vitiello, & Hoagwood, 2004). Although ADHD symptom reduction was greatest in the two stimulant-treated groups at the end of the 14-month treatment, both medication- and non–medication-treated groups had equal but limited benefit at 24 and 36 months after randomization. Although evidence for short-term gains in arithmetic performance exists (Pelham, Bender, Caddell, Booth, & Moorer, 1985), other evidence (Charles, Schain, & Guthrie, 1979) points to a lack of differences in long-term academic achievement between treated and untreated ADHD children.

Despite the breadth and depth of the stimulant treatment literature showing robust evidence of an acute powerful "treatment that works," most long-term studies continue to present stiff challenges. Randomization cannot be maintained over years, so that selection biases confound the interpretation of the results from long-term follow-up programs. Observations lasting years lose random assignment, fail to maintain checks on treatment adherence, and experience high attrition rates. Studies continue to use global improvement rather than objective measures of ADHD symptoms to optimize individual medication doses. No mention is made of whether the time of dosing is controlled. The majority of drug studies covered by reviews lasted 6 weeks or less, too brief to generalize to typical medication treatments, which average 3 years. Since no common definition of a categorical treatment responder has been established, it has been difficult to interpret meta-analytic research looking across studies for identical response patterns in children.

LARGE RANDOMIZED CONTROLLED TRIALS OF STIMULANT MEDICATION

Generalizability and statistical power were limited in earlier ADHD treatment studies because they were conducted at one site, often with a clinical population with local characteristics. A new era in ADHD treatment studies was ushered in during the early 1990s, when clinical trial science was applied to the ADHD field. First NIMH, and then the pharmaceutical industry, began to employ multisite clinical trial designs to determine the safety and efficacy of stimulants. This allowed investigators to recruit subjects from several performance sites to obtain the sample size needed to make estimates of the efficacy of the drug. Extending the duration of stimulant drug exposure became a key design goal in these large multisite clinical trials. Up to 1995, only 22 published stimulant

studies lasted longer than three weeks (Schachar & Tannock, 1993). The few long-duration stimulant studies published before the 1990s had been constrained by their retrospective methods, lack of standard outcome measures, restrictive inclusion criteria that rejected patients with comorbid disorders, irregular prescribing patterns (Sherman, 1991), and lack of compliance measures (Richters et al., 1995).

The MTA Study was designed to address most of the shortcomings of the pre-1990 ADHD treatment trials. It established a standard in RCT sample size, diagnostic rigor, quality control, use of standardized measures, parallel design, and randomization that the large pharmaceutical stimulant trials followed beginning in the late 1990s. The MTA Study recruited almost 600 children with ADHD from seven performance sites in the United States and Canada using uniform diagnostic criteria, randomized these subjects to different treatments, and then maintained them for 14 months on those treatments, employing intent-to-treat methods not previously used for this population. The study goal was to compare the relative effectiveness of four randomly assigned 14-month treatments: algorithmic medication management (MedMgt), behavioral treatment (Beh), combination of MedMgt and Beh (Comb), and community comparison group (CC) receiving treatment as usual (Arnold et al., 1997). The study questions included the following: (a) Do Beh and MedMgt treatments result in comparable levels of improvement over time? (b) Do participants assigned to Comb show greater improvement over time than those assigned to either MedMgt or to Beh? and (c) Do participants assigned to any of the three MTA intensive treatments show greater improvement over time than those assigned to treatment as usual in the community (CC)? Assessment points for measured outcomes were evaluated in multiple domains before, during, and at the end of treatment (with Comb and MedMgt subjects on medication at time of assessment).

Children randomized to medication management alone (MedMgt, $N = 144$) or to combined treatment (Comb, $N = 145$) began treatment with a 28-day, double-blind, placebo-controlled titration to identify each child's optimal MPH dose. Due to its 3- to 4-hour duration of action, immediate-release MPH (IR-MPH) and placebo were administered three times daily (Greenhill et al., 1996, 2001a). Medication conditions were switched daily to reduce error variance. Parents and teachers rated ADHD symptoms and impairment daily. During titration, a repeated-measures ANOVA revealed a main effect of MPH/placebo dose with greater effects on teachers' ratings ($F(3) = 100.6$, $N = 223$, $p = .0001$; effect sizes 0.8 to 1.3) than on parents' ratings ($F(3) = 55.61$, $N = 253$, $p = .00001$; effect sizes 0.4 to 0.6). Dose did not interact with between-subjects factors (period, dose order, comorbid diagnosis, site, or treatment group). Drug-related adverse events were reported more often by parents than by teachers, who rated irritability highest on placebo. The distribution of the best MPH starting doses determined during titration (10 to 50 mg/day), response rate (77%), and adverse event profile across six sites and multiple subgroups suggest that MPH titration in office practice should explore MPH's full dosage range in 7- to 10-year-old children over 25 kg in weight. Parent weekend symptom ratings showed daytime drug effects, but not as clearly as weekday after-school ratings. Nonresponders to MPH were older, had less severe symptoms, and were medication naïve.

Data were analyzed through intent-to-treat random-effects regression. All four groups at 14 months (end of the active treatment period) showed sizable reductions in symptoms over time, with significant differences among them in degrees of change. For ADHD symptoms, children in the combined and medication management groups showed significantly greater improvement than those given intensive behavioral treatment or community care. However, combined and medication management treatments did not differ significantly for ADHD symptoms. As measured by teacher-rated social skills, parent–child relations, and reading achievement, combined treatment proved significantly better than other treatments in reducing symptom scores for internalizing symptoms. The MTA Study medication strategies were superior to treatment as usual in the community, despite the fact that two thirds of community-treated subjects received medication during the study period. The combined treatment did not yield significantly greater benefits than medication management for core ADHD symptoms, but it may have provided modest additional advantages for non-ADHD-symptom and positive functioning outcomes.

The MTA is the largest and most methodologically sophisticated randomized multisite pediatric ADHD treatment study to date that includes monomodal and combined treatments. These therapeutic methods had been previously shown effective in

simpler two-arm (active vs. placebo) controlled studies (Pelham, 1989; Pelham & Murphy, 1986). Due to its size, the MTA Study was able to address comparative treatment questions. It concluded that stimulant medication efficacy can be realized across diverse settings and patient groups, is more effective than behavioral modification for core ADHD symptoms and can be maintained during chronic therapy lasting more than a year.

The MTA replicated findings from smaller long-duration stimulant trials—the 102-child New York/Montreal Study (Klein, Abikoff, Hechtman, & Weiss, 2004), the 91-child Toronto study (Schachar, Tannock, Cunningham, & Corkum, 1997), and the 62-child Gillberg (Gillberg et al., 1997) study. Collectively, these smaller multisite studies show a persistence of medication effects over time. Within-subject effect sizes reported 12 to 24 months following the MPH treatment resembled those previously reported in short-duration studies (Elia, Borcherding, Rapoport, & Keysor, 1991; Thurber & Walker, 1983). Domain of greatest improvement differed among studies, with one (Gillberg et al., 1997) showing greater effects at home and another (Schachar et al., 1997) showing greater effects at school. The total mean MPH daily dose reported by the three long-duration studies ranged between 33 and 37.5 mg. The one DEX study that examined the effects of different doses reported a mean dose half of this level, agreeing with the general ratio of DEX to MPH doses. Persistent stimulant drug side effects and assignment to placebo treatment were associated with dropout. Fortunately, the attrition rate from placebo assignment was low, allowing ample time for standard 8-week efficacy trials to be conducted.

Long-term follow-up data from the MTA are not as promising. A 2007 study that followed children who had participated in the MTA Study found that 3 years after the trial began the initial advantages of medication management alone or in combination with behavioral treatment over purely behavioral or routine community care had waned after 14 months of controlled treatment had ended (Jensen et al., 2007a). Additional follow-up studies reporting key outcomes at 6 and 8 years demonstrated that despite overall maintenance of improvement in functioning relative to baseline (pretreatment), the MTA group as a whole was functioning significantly less well than the non-ADHD classmate sample recruited at 24 months (Molina et al., 2009). As the authors suggested, these findings provide evidence that the differential effects of the ADHD treatments, evident when the interventions were delivered, attenuated when the intensity of treatment was relaxed.

CURRENT PSYCHOPHARMACOLOGICAL AGENTS' EFFICACY AND UTILITY

Two groups of stimulants are currently approved by the FDA for ADHD treatment in children. These are available in both brand and generic, and in immediate-release (short-duration) and long-duration formulations: the amphetamines (Adderall, Dexedrine, Vyvanse) and the methylphenidates (Concerta, Metadate ER, Metadate CD, Methylin ER, Ritalin, Ritalin SR, Ritalin LA, Focalin, Daytrana Patch, Quillivant XR). Characteristics of these stimulants can be found in Table 4.1. DEX and MPH are structurally related to the catecholamines (dopamine [DA] and norepinephrine [NE]). The term *psychostimulant* used for these compounds refers to their ability to increase central nervous system activity in some but not all brain regions.

Compared with placebo, psychostimulants have a significantly greater ability to reduce ADHD symptoms, such as overactivity (e.g., fidgetiness and off-task behavior during direct observation), and to eliminate behavior that causes disruptions in the classroom (e.g., constant requests of the teacher during direct observation; Jacobvitz et al., 1990). In experimental settings, stimulants have been shown to improve child behavior during parent–child interactions (Barkley & Cunningham, 1979) and problem-solving activities with peers (Whalen et al., 1989). The behavior of children with ADHD has a tendency to elicit negative, directive, and controlling behavior from parents and peers (Campbell, 1973). When these children are placed on stimulants, their mothers' rate of disapproval, commands, and control diminishes to the extent seen in mothers' of non-ADHD children (Barkley & Cunningham, 1979; Barkley et al., 1984; Humphries, Kinsbourne, & Swanson, 1978). In the laboratory, stimulant-treated ADHD children demonstrate major improvements during experimenter-paced continuous performance tests (Halperin, Matier, Bedi, Sharma, & Newcorn, 1992), paired-associate learning, cued and free

TABLE 4.1 Stimulant Drugs with FDA Indication for ADHD

Medication (Brand Name)	*Available Dose of Preparation*	*Starting Dose/Maximum Dose*	*Indicated Age (Years) for Psychiatric Use*	*Duration of Action (hours)*
Methylphenidate (MPH)				
Short Acting				
Methylphenidate HCl (*Ritalin*)	5-, 10-, 20-mg tabs	2.5 mg b.i.d./30 mg/day	6+	3–5
Methylphenidate HCl Chewable Tabs (*Methylin*)	2.5-, 5-, 10-mg tabs	2.5 mg b.i.d./30 mg/day	6+	3–5
Methylphenidate HCl Solution (*Methylin solution*)	5 mg/5 mL, 10 mg/5 mL	2.5 mg b.i.d./30 mg/day	6+	3–5
Dexmethylphenidate HCl (*Focalin*)	2.5-, 5-, 10-mg tabs	2.5 mg b.i.d./20 mg/day	6+	5–6
Intermediate Acting				
Methylphenidate HCl Extended-Release (*Metadate ER*)†	10-, 20-mg tabs	10 mg AM/60 mg/day	6+	4–8
Methylphenidate HCl Extended-Release (*Methylin ER*)†	10-, 20-mg tabs	10 mg AM/60 mg/day	6+	4–8
Methylphenidate HCl Extended-Release (*Ritalin SR*)†	20-mg tabs	20 mg AM/60 mg/day	6+	4–8
Long Acting				
Methylphenidate HCl Extended-Release (*Ritalin LA*)‡	10-, 20-, 30-, 40-mg caps	10 mg AM/60 mg/day	6+	6–8
Methylphenidate HCl Extended-Release (*Metadate CD*)‡	10-, 20-, 30-, 40-, 50-, 60-mg tabs	10 mg AM/60 mg/day	6+	6–8
Methylphenidate HCl Extended-Release (*Concerta*)†	18-, 27-, 36-, 54-mg tabs	18 mg AM/54 mg/day or 72 mg/day in children 12+	6+	10–12
Dexmethylphenidate beaded (*Focalin XR*)‡*	5-, 10-, 15-, 20-, 25-, 30-, 35-, 40-mg caps	5 mg AM/30 mg/day	6+	8–12
Methylphenidate Extended-Release Solution (*Quillivant XR*)	25 mg/5 mL	20 mg AM/60 mg/day	6+	8–12
Methylphenidate Transdermal Patch (*Daytrana*)	12.5 cm^2 (10 mg), 18.75 cm^2 (15 mg), 25 cm^2 (20 mg), 37.5 cm^2 (30 mg)	10 mg AM/9 hrs. (off 15 hrs)/ 30 mg/day	6+	10–12 *Note*: Apply 2 hrs. before desired effect; drug effects may persist up to 5 hrs after patch removal

Amphetamines				
Short Acting				
Mixed Amphetamine Salts (*Adderall*)	5-, 7.5-, 10-, 12.5-, 15-, 20-, 30-mg tabs	2.5 mg b.i.d./40 mg/day	3+	4–6
Dextroamphetamine Sulfate (*Dexedrine*)	5-, 10-mg tabs	2.5 mg b.i.d./40 mg/day	3+	4–6
Dextroamphetamine Sulfate Liquid (*ProCentra*)	5 mg/5 mL	2.5 mg b.i.d./40 mg/day	3+	4–6
Methamphetamine (*Desoxyn*)	5-mg tabs	5 mg b.i.d./25 mg/day	6+	4–6
Intermediate Acting				
Dextroamphetamine Sulfate (*Dexadrine Spansule*)	5-, 10-, 15-mg caps	5 mg AM/40 mg/day	3+	6–8
Long Acting				
Mixed Amphetamine Salts Long Acting (*Adderall XR*)[‡*]	5-, 10-, 15-, 20-, 25-, 30-mg caps	5 mg AM/30 mg/day or 40mg/day in children 12+	6+	8–10
Lisdexamfetamine (*Vyvanse*)[¥*]	20-, 30-, 40-, 50-, 60-, 70-mg caps	30 mg AM/70 mg/day	6+	Up to 12

Safety—Black box warning: All stimulants have increased risk of abuse

Safety—General warnings and precautions (Non-black box): All stimulants have increased risk of the following

- Serious Cardiovascular Events
- Increase in Blood Pressure
- Psychiatric Adverse Events
- Seizures
- Visual Disturbance
- Tics
- Long-Term Suppression of Growth

[†] Must be swallowed (not crushed or chewed)

[‡] Capsule can be opened and medication sprinkled on applesauce

[¥] Can be dissolved in liquid

[*] FDA approved for treating adult ADHD

recall, auditory and reading comprehension, spelling recall, and arithmetic computation (Pelham & Bender, 1982; Stephens, Pelham, & Skinner, 1984). Some studies show correlations between plasma levels of MPH and performance on a laboratory task (Greenhill, 1995), but plasma levels rarely correlate with clinical response. Likewise, hyperactive conduct-disordered children and preadolescents observed in structured and unstructured school settings show reductions in aggressive behavior when treated with stimulants (Hinshaw, 1991). Stimulants can also reduce the display of covert antisocial behaviors such as stealing and property destruction (Hinshaw, Heller, & McHale, 1992).

Psychostimulants are thought to block the reuptake of dopamine and norepinephrine into the presynaptic neuron in the central nervous system and increase the concentration of these neurotransmitters in the interneuronal space. Changes in a single neurotransmitter that regulate an ADHD child's under- or over-aroused central nervous system have been discounted (Solanto, 1984; Zametkin & Rapoport, 1987). A two-part theory of stimulant action has been postulated (McCracken, 1991) in which stimulants increase DA release, producing enhanced autoreceptor-mediated inhibition of ascending DA neurons, while simultaneously increasing adrenergic-mediated inhibition of the noradrenergic-locus coeruleus via epinephrine activity. This theory awaits confirmation from basic research in animals and imaging studies in humans.

One of the most important findings in the stimulant treatment literature is the high degree of short-term efficacy for behavioral targets, with weaker effects for cognition and learning. Conners (personal communication, 1993) notes that 0.8, 1.0, and 0.9 effect sizes are reported for behavioral improvements in type 4 meta-analytic reviews of stimulant drug actions (Kavale, 1982; Ottenbacher & Cooper, 1983; Thurber & Walker, 1983). These behavioral responses to stimulant treatment, when compared with placebo, resemble the treatment efficacy of antibiotics. Less powerful effects are found in laboratory measures of cognitive changes, in particular on the continuous performance task, for which effect sizes of these medications range between 0.6 and 0.5 for omissions and commissions, respectively, in a within-subject design (Milich, Licht, Murphy, & Pelham, 1989) and 0.6 and 1.8 in a between-subject study (Schechter & Keuezer, 1985).

Psychostimulants have continued to show behavioral efficacy in the type 1 RCTs published over the past 10 years (Table 4.2). These modern-day controlled trials have matured with the field and now use multiple-dose conditions with multiple stimulants (Newcorn et al., 2008), parallel designs (Spencer et al., 1995), and normalization as a common definition of response (Abikoff & Gittelman, 1985; Rapport, Denney, DuPaul, & Gardner, 1994). These studies assess psychostimulant use in special ADHD populations, including adolescents (Klorman et al., 1990), adults (Spencer et al., 1995), children with intellectual disabilities (Horn et al., 1991), and subjects with comorbid anxiety disorders and other internalizing disorders and with tic disorders (Gadow, Sverd, Sprafkin, Nolan, & Ezor, 1995). As shown in Table 4.2, 70% of ADHD subjects respond to stimulants and less than 13% respond to placebo (Greenhill et al., 2001b).

Studies have also attempted to learn more about stimulant nonresponders. Some drug trials (Douglas, Barr, Amin, O'Neill, & Britton, 1988) report a 100% response rate in small samples in which multiple MPH doses are used. Others find that a trial involving two stimulants effectively lowers the nonresponse rate. Elia and colleagues (1991) reduced the 32% nonresponse rate to a single psychostimulant to less than 4% when members of both stimulant classes, DEX and MPH, were titrated sequentially in the same subject. However, the rate of medication nonresponse might be higher if children with comorbidity are included in the sample. Finally, a few studies have used the double-blind or single-blind placebo discontinuation models to determine whether the child continues to respond to stimulants after being treated for 1 year or more. One study found that 80% of ADHD children relapsed when switched single blind from MPH to a placebo after 8 months of treatment (H. Abikoff, personal communication, 1994). Even so, these observations about the "rare nonresponder" do not address the rate of placebo response. Few, if any, of the current RCTs are parallel designs, which can evaluate whether placebo response emerges at some point over the entire drug trial. Few treatment studies prescreen for placebo responders, so the numbers of actual medication responders in any sample of ADHD children might be closer to 55%, not the 75% to 96% often quoted. Furthermore, these estimates apply to group effects and do not inform the clinician about the individual patient.

TABLE 4.2 Controlled Studies Showing Stimulant Efficacy in ADHD Drug Treatments (N = 2,234)

Study (Year)	*N*	*Age Range (Years)*	*Design*	*Drug (dose)*	*Duration*	*Response*	*Comment*
Abikoff & Gittleman (1985)	28	6–12	ADHD vs. normal controls	MPH (41 mg/day) PB	8 weeks	80.9%	ADHD children normalized
Abikoff et al. (2004)	103	7–9	ADHD	MPH (33.7 mg) t.i.d.	2 years	100%; SD 2.7	No advantage to combination treatment
Barkley et al. (1989)	74	6–13	X-over (37 agg & 37 non agg)	MPH (0.3, 0.5) PB	4 weeks	80%	Agg responsive to MPH
Barkley et al. (1991)	40	6–12	X-over (23 ADHD & 17 ADHD-W)	MPH (5, 10, 15 mg b.i.d.) PB b.i.d.	6 weeks	ADHD 95%; ADHD-W 76%	Fewer children with ADHD-W respond, need low dose
Biederman et al. (2007b)	290	6—2	Parallel	LDX (30, 50, or 70 mg/day) PB	4 weeks	Effect size > 1.2 for all dose ranges	Greatest effect size seen in the 70-mg group
Castellanos et al. (1997)	20	6–13	X-over (Pts. with ADHD + Tourette's)	MPH (45 mg bid) DEX (22.5 mg bid)	9 weeks	ADHD + TS	Emergence of tics was dose-related.
Douglas et al. (1988)	19	7–13	X-over	MPH (0.15, 0.3, 0.6) PB	2 weeks	100%	Linear D/R relationships
Douglas et al. (1995)	17	6–11	X-over	MPH (0.3, 0.6, 0.9) PB	4 weeks	Behavior 70%	No cognitive toxicity at high doses, linear D/R curves
DuPaul & Rapport (1993)	56	6–12	X-over 31 ADHD, 25 normal	MPH (20 mg/day) PB bid	6 weeks	Behavior 78%, attention 61%	MPH can normalize classroom beh; 25% of ADHD subjects did not normalize academics
DuPaul et al. (1994)	40	6–12	X-over 12 high anxiety 17 mid anxiety 11 low anxiety	MPH (5, 10, 15 mg/day); PB single dose	6 weeks	High 68% Nortriptyline Mid 70% Nortriptyline Low 82% Nortriptyline	25% of internalizing group deteriorated ADHD meds
Elia et al. (1991)	48	6–12	X-over	MPH (0.5, 0.8, 1.5) DEX (0.25, 0.5, 0.75) PB bid	6 weeks	MPH 79% DEX 86%	Response rate for two stimulants: 96%

(*continued*)

TABLE 4.2 (continued)

Study (Year)	N	Age Range (Years)	Design	Drug (dose)	Duration	Response	Comment
Gadow et al. (1995)	34	6–12	ADHD + tic disorder	MPH (0.1, 0.3, 0.5) PB bid	8 weeks	MPH 100%	No responders to beh; MD's motor tic ratings show 2 min. increases on drug; only shows effects of 8 wks. of txt
Gillberg et al. (1997)	62	6–12	Parallel	MAS (17 mg) PB b.i.d.	60 weeks	70%; 27-40% improve	No dropouts but only 25% PB group at 15-mo assessment
Greenhill et al. (2001)	277	6–12	Parallel	Long-acting MPH (Metadate CD) PB	3 weeks	70%	Mean total dose: 40 mg/day; FDA registration
Greenhill et al (2002)	321	6–12	Parallel	MPH-MR (*Metadate-ER*) (20, 60 mg/day) PB tid	3 weeks	MPH-MR 64%; PB 27%	Mean MPH-MR daily dose = 40.7 mg (1.28 mg/kg per day)
Greenhill et al. Preschool ADHD Treatment Study (PATS) (2006a)	165	3–5.5	X-over	IR-MPH (1.25, 2.5, 5, 7.5 mg t.i.d.); PB t.i.d.	70 weeks	88%	Optimal IR-MPH dose = 14.22 ± 8.1 mg/day (0.7 + 0.4 mg/kg per day); treatment effect sizes < than in school-age children
Greenhill et al. (2006b)	165	6–17	Parallel	d-MPH-ER (*Focalin LA*) (5–30 mg/day) PB qday	7 weeks	d-MPH-ER 67.3%; PB 13.3%	Mean d-MPH-ER daily dose = 24 mg
Klein et al. (1997)	84	12–18	Parallel	MPH (1.0) b.i.d.	5 weeks	MPH 9–78% PB 9–29%	MPH reduced ratings of antisocial beh
Klorman et al. (1990)	48	6–15	X-over	MPH (0.26) PB t.i.d.	6 weeks	MPH 60%	Fewer med benefits in adolescents
McGough et al. (2006)	97	6–17	X-over	MPH transdermal system on 9 hrs/day (12.5, 18.75, 25, 37.5 cm^2); PB	2 weeks	79.8%	MPH transdermal system is well tolerated and significantly more efficacious than PB
MTA Cooperative Group (1999)	579	7–9	Parallel	MPH (<0.8) t.i.d.	4 weeks (14 months)	MPH 77% DEX 10% None 13%	Titration trial for multisite multimodal study; full study data for 288 on 38.7 mg MPH
Musten et al. (1997)	31	4–6	X-over	MPH (0.3, 0.5) PB b.i.d.	3 weeks	MPH > NA	MPH improves attention in preschoolers
Pelham et al. (1990)	22	8–13	X-over	MPH 10 mg b.i.d.; PB b.i.d.; DEX spansule 10 mg; PEM 56.25 qd	24 days	Stim 68%	DEX span, PEM best for beh 27% did best on DEX; 18% on SR; 18% on PEM; 5% on MPH id.

Pelham et al. (1995)	28		X-over	PEM (18.75, 37.5, 75, 112.5 mg); PB qd	7 weeks	PEM 89%; PB 0%	PEM dose ≥ 37.5 mg/d lasts 2–7 hrs; efficacy and time course = MPH
Rapport et al. (1988)	22	6–10	X-over	MPH (5, 10, 15 mg) PB	5 weeks	72%	MPH response same in home and school
Rapport et al. (1994)	76	6–12	X-over	MPH (5, 10, 15, 20 mg) PB	5 weeks	94% behavioral; 53% attention	MPH normalizes beh> academics; higher doses better, linear D/R curve
Schachar et al. (1997)	91	6–12	Parallel	MPH (33.5 mg) PB b.i.d.	52 weeks	0.7 SD effect size	15% side effects: affective, over-focusing led to dropouts
Spencer et al. (1995)	23	18–60	X-over	MPH (1.0 mg/kg/day)	7 weeks	MPH 78% PB 4%	MPH at 1 mg/kg per day produces improvement in adults equivalent to that seen in children
Swanson et al. (1998)	29	7–14	X-over	MAS (5, 10, 15, 20); MPH; PB	7 weeks	100%	Adderall peaks at 3 hrs; MPH at 1.5 hrs
Tannock et al. (1995a)	40	6–12	X-over 17 ADHD-ANX	MPH (0.3, 0.6)	2 weeks	70%	Activity level better in both groups; working memory not improved in anxious kids
Tannock et al. (1995b)	28	6–12	X-over	MPH (0.3, 0.6); PB	2 weeks	70%	Effects on behavior D/R curve linear, but effects on response inhibition U-shaped suggest adjustment dose on objective measures
Taylor et al. (1987)	38	6–10	X-over	MPH (0.2–1.4); PB	6 weeks	58%	Severe ADHD symptom, better response
Whalen et al. (1989)	25	6.3–12	X-over	MPH (0.3,0.5)	5 weeks	48–72%	MPH helps, not normalizes, peer status
Wigal et al. (2004)	132	6–17	Parallel	d-MPH; d,l-MPH; PB b.i.d.	4 weeks	d-MPH 67%; d,l-MPH 49%	Average d-MPH dose (18.25 mg) is as safe and effective as half of the average d,l-MPH dose (32.14 mg)
Wilens et al. (2006)	177	13–18	Parallel	OROS-MPH (18, 36, 72 mg qd); PB	2 weeks	OROS-MPH 52%: PB 31%	OROS-MPH is well tolerated and effective in adolescents at up to 72 mg daily dose
Wolraich et al. (2001)	277	6–12	Parallel	OROS MPH (36 mg); MPH t.i.d.; PB	4 weeks	62%	Concerta rated effective by teachers and parents

Doses listed as mg/kg per dose, and medication is given twice daily unless otherwise stated.

PB, placebo; X-over, crossover design; ANX, anxiety; MPH, methylphenidate; DEX, dextroamphetamine; PEM, pemoline; MAS, mixed amphetamine salts (*Adderall*); mg/kg per day, dosage in mg/kg per day; Agg, aggression; ADHD-W, ADD without hyperactivity; beh, behavior; att, attention; FDA, Food and Drug Administration; D/R curve, dose-response curve.

USE OF PSYCHOSTIMULANTS IN CHILDREN YOUNGER THAN 6 YEARS

The signs and symptoms of ADHD, such as particularly pronounced motor activity, excessive climbing, aggressivity, and destructiveness, may be evident before age three. These signs can disrupt family life and make nursery school attendance difficult. Campbell found that many hyperactive preschoolers did not "grow out of" this behavior but maintained their hyperkinesis in grade school (Campbell et al., 1977). More recently, Lahey and his colleagues conducted an 8-year follow-up study in 118 children, aged 4 to 6 years, who initially met *DSM-IV* criteria for ADHD. The study found that 81% of children with ADHD combined type and 73.9% of those with predominantly hyperactive subtype continued to meet criteria for any ADHD subtype, (Lahey et al., 2005). Follow-up of the NIMH Preschool ADHD Treatment Study (PATS) sample of children ages 3 to 5 some 6 years later confirmed the long-term stability of the ADHD diagnosis beginning in the preschool phase of development (Riddle et al., 2013). Even though these early ADHD symptoms resemble the behaviors among older ADHD patients, the diagnostic manuals give little guidance about how to determine the validity of the ADHD diagnosis in the preschool years. School-age norms gathered on standard teacher global rating forms, such as the Conners Teacher Questionnaire, have not included preschoolers in the past (Conners, personal communication).

Until recently, there were only a handful of small, single-site, published studies addressing stimulant treatment in preschoolers. For the amphetamines, there is only one single-case intensive study suggesting that DEX reduces temper outbursts in a toddler (Speltz et al., 1988). MPH treatment studies have found that the drug ameliorates mother–child interactions (Barkley, 1988) in a linear dose-response fashion, perhaps related to increasing child compliance and decreased symptomatic intensity. No pharmacokinetic studies have been done in this age group to determine whether younger children metabolize psychostimulants differently than older children.

A comprehensive review of preschool stimulant treatment studies (Connor, 2002) identified nine controlled studies ($N = 206$) of stimulants in children under the age of 6 (Barkley, 1988; Barkley et al., 1984; Conners, 1975; Handen et al., 1999; Mayes et al., 1994; Musten et al., 1997; Schleifer et al., 1975). MPH doses ranged from 2.5 to 30 mg/day (0.15 to 1.0 mg/kg per day). Most of the studies showed MPH efficacy at weight-adjusted doses comparable to those reported for older school-age children, producing improvements in structured situations but not in free play (Schleifer et al., 1975). These studies, particularly if they involved preschoolers with developmental delays, suggested that stimulants may produce higher rates of side effects, including tearfulness and irritability, than would be expected in school-age children (Handen et al., 1999). This suggests that preschoolers with ADHD should be started on low MPH doses.

Interpretations of these early data are difficult because of methodologic differences among the nine studies, which used very different inclusion/exclusion criteria, diagnostic definitions, ratings forms, and study designs, thus making a meta-analysis impossible. Unlike the increased rate of stimulant use in adolescents, and the relatively stable use among 6- to 12-year-olds, the rate of stimulant prescriptions written for preschool children declined between 1996 and 2008 (Zuvekas et al., 2012).

To address the lack of methodologically sound data on the safety and efficacy of MPH in preschool ADHD children, the NIMH launched a six-performance-site, randomized, placebo-controlled trial of MPH, the PATS. This study recruited 303 children (3 to 5 years old); 279 of their parents were entered into a 10-week course of behavior modification training. For one third of these children, ADHD symptoms improved so dramatically with behavior therapy alone that they did not progress to the medication phase of the study. Of the children who did not respond to parent training, 183 families agreed to enter the PATS medication protocol. Of these, 165 families were randomized into a double-blind, placebo-controlled, crossover design dose-optimization study that began with a 1-week, open, stepwise safety phase exposing all the preschoolers to the drug before their entry into the double-blind protocol. The children were given medication (placebo, 1.25, 2.5, 5, or 7.5 mg) capsules three times a day, and the dose was switched each week. Blind raters selected the MPH dose for each child that produced the best compromise between lowering ADHD symptoms without creating significant adverse events (Kollins et al., 2006). The mean "best" total daily MPH dose for all the preschoolers as determined by the raters was 14 mg, or 0.75 mg/kg per day, which was lower than the mean dose of

1.0 mg/kg per day MPH reported by the MTA Study (Greenhill et al., 2006a).

On their "best" dose, the 165 preschoolers in the PATS showed a significant decrease in ADHD symptoms compared with their response to placebo. A subset of 114 children was then randomized to a double-blind, parallel-design study, with half randomized to their best MPH dose and the other half to placebo. The teacher reports showed significant continued improvements for those on MPH. However, 11% of PATS subjects discontinued the trial because of MPH-associated adverse events, which is far more than the 2% of subjects who stopped the MTA Study for similar reasons. The preschool group showed a significantly higher rate of irritability, decreased appetite, delay in sleep onset, and proneness to crying in the MPH condition than they did on placebo (Wigal et al., 2006). An open pharmacokinetic pilot study done on a small subset of PATS patients suggested that preschoolers with ADHD show significantly lower MPH clearance than do school-age children even when corrected for weight (Wigal et al., 2006).

USE OF PSYCHOSTIMULANTS IN THE TREATMENT OF ADULTS WITH ADHD

Until recently, the prevalence and severity of ADHD in adults, as well as indications for treatment, were not clear. Contrary to the assumption that children outgrow their childhood problems, ADHD symptoms persist into adulthood. From 2% (Mannuzza et al., 1993) to 27% of patients (Barkley, Fischer, Smallish, & Fletcher, 2002) are estimated to continue having the disorder into the adult life range. Epidemiologic data from the National Comorbidity Study that sampled 3,199 individuals, aged 18 to 44 years, estimated the point prevalence of adult ADHD to be 4.4% (Kessler et al., 2006).

As ADHD problems from childhood onset persist into adolescence, the impairment from the disorder continues. Almost 30% of ADHD adolescents fail a course in school; 46% are suspended; and most have difficulties taking notes, planning assignments, writing, and transitioning from homework to self-motivated study, resulting in academic underachievement. As adults, individuals with childhood histories of ADHD continue to have significant problems in both their professional and personal lives. When left untreated, this population tends to have poorer educational performance, is more likely to be fired from or impulsively quit a job, makes more frequent job changes, and earns less income (Kotsopoulos et al., 2013). In addition, this population endorses having more psychological distress, more marriages, poorer driving skills, and more motor vehicle accidents (Biederman et al., 2006; Merkel et al., 2013; Murphy & Barkley, 1996). In a study of Swedish national registers, Lichtenstein and colleagues (2012) compared the rates of criminality among patients with ADHD both on and off medication. This study found that rates of criminality were lower during periods when this cohort was receiving ADHD medication (reduction of 32% in the criminality rate for men and 41% for women).

If adolescents with ADHD begin to smoke, they have much more difficulty stopping. Substance use disorders are also high in adults who had suffered from ADHD as children, ranging from 18% (Mannuzza et al., 2002) to 43% (Barkley et al., 2002). When adolescents with ADHD begin to drive, they are more likely than their peers to get speeding violations, to have their licenses revoked, and to be involved in motor vehicle accidents with significant damage to themselves and their vehicles (Barkley et al., 1993, 1996). In his Milwaukee follow-up study, Barkley reported that 40% of children with ADHD continue to have impairing ADHD as adults. If they also had childhood comorbid CD, their rates of other disorders in adulthood greatly increase, including depression (27% more than ADHD children without CD) and substance use/abuse disorders (up to 24%), and 21% have personality disorders, particularly antisocial personality disorder (up to 25%) (Fischer et al., 2002).

As adults, patients with childhood histories of ADHD continue to have problems (Barkley et al., 1990; Biederman et al., 1996; Mannuzza et al., 1998; Weiss et al., 1985). Between 66% and 85% were reported to suffer from at least one impairing symptom of ADHD. Although 80% of parents report that their older adolescents show persistence of ADHD symptoms from childhood, including impulsiveness, easy distractibility, inattentiveness, easily bored attitude, and restlessness, other types of impairments are also noted during interviews with the parents. Compared with controls, the index group report fewer years of education completed, a higher incidence of antisocial personality disorder, lower scores on clinician-rated global assessment rating scales,

more complaints of restlessness, as well as sexual and interpersonal problems.

The first stimulant treatment studies of adults with ADHD did not show the high response rates seen in children. Mattes and Boswell (Mattes, Boswell, & Oliver, 1984) reported little benefit from MPH, but others have found more robust effects (Ratey, Greenberg, & Lindem, 1991; Wender, Reimherr, & Wood, 1981). As a result, other drugs have been tested in adults with ADHD symptoms, including fluoxetine (Sabelsky, 1990), nomifensine (Shekim, Masterson, Cantwell, Hanna, & McCracken, 1989), pargyline (Wender, Wood, Reimherr, & Ward, 1994), bupropion (Wender & Reimherr, 1990), the monoamine oxidase (MAO) inhibitor selegiline (Ernst et al., 1995), and the long-acting methamphetamine compound desoxyn gradumets (Wender, 1994). Whereas the nicotinic analogue ABT 418 significantly reduced ADHD symptoms (Pelham et al., 2000), the antinarcoleptic modafinil (Provigil) failed to separate from placebo in multisite controlled trials of three doses (100, 200, and 400 mg; Cephalon press release, July 31, 2000). Wilens and Biederman (1992) pointed out that the initial studies of stimulant-treated adults were inconclusive due to the low stimulant dosages used, the high rate of comorbid disorders in the patients, and/or the lack of a clear childhood ADHD history. A number of these studies used self-report outcome measures, even though adult ADHD patients appear to be unreliable reporters of their own behaviors. When the clinicians served as reporters and weight-adjusted doses of stimulants were used, the adult response rates were just as elevated as those in school-age children.

The efficacy of MPH (Spencer et al., 1995), mixed salts of amphetamine (MAS) (Spencer et al., 2001), and ATX (Michelson et al., 2003; Spencer et al., 1998) in adults has been established by double-blind, placebo-controlled RCTs. MPH's efficacy was shown in a 7-week, double-blind comparison of MPH (1 mg/kg per dose) and placebo carried out in 23 adult ADHD patients; 78% showed improvement on MPH versus 4% who responded to placebo (Spencer et al., 1995). The MPH response was independent of gender, comorbidity, or family history of psychiatric disorders. At the target dose of 1.0 mg/kg side effects included loss of appetite, insomnia, and anxiety. MAS efficacy was also ascertained in a 7-week, randomized, double-blind, placebo-controlled trial for 27 adults meeting *DSM-IV* criteria for ADHD of childhood onset with symptoms persistent into adulthood (Spencer et al., 2001). MAS treatment with a mean b.i.d. dose of 54 mg was associated with a 42% drop in ADHD symptom severity, with improvement seen in the first week. Finally, ATX treatment was associated with a significant improvement in ADHD symptoms as compared to placebo over a 10-week study period (Michelson et al., 2003; Spencer et al., 2001).

Currently, the following medications are FDA approved for the treatment of ADHD in adults: ATX, mixed salts of amphetamine XR (Adderall XR), dexmethylphenidate XR (Focalin XR), lisdexamfetamine (Vyvanse), OROS-MPH (Concerta), and liquid MPH (Quillivant XR). Clinicians should be cautious about prescribing psychostimulants for adults with a comorbid substance abuse disorder. In these patients, it is preferable to use medications with lower abuse potential, such as ATX.

STIMULANT DRUGS

MPH, or methyl a-phenyl-2-piperidineacetate hydrochloride, is the active ingredient in the majority of stimulant medications prescribed in the United States. With the exception of the two *d*-methylphenidate (Focalin, Focalin XR) products, MPH's racemic mixture, composed of the *d*- and *l*-threo enantiomers, is used. The *d*-threo enantiomer is more pharmacologically active than the *l*-threo enantiomer. After the immediate-release tablet is swallowed, MPH absorption into the systemic circulation is rapid, so that effects on behavior can be seen within 30 minutes. Plasma concentration reaches a peak by 90 minutes, with a mean half-life of about 3 hours and a 3- to 5-hour duration of action. MPH is metabolized extrahepatically via de-esterification to alpha-phenyl-piperdine acetic acid (PPA, ritalinic acid), an inactive metabolite. About 90% of radiolabeled MPH is recovered from the urine.

Most children taking one IR-MPH dose just after breakfast will require a second dose at lunch (which for young children must be given by the school nurse) and a third dose after coming home from school in the afternoon to prevent loss of effectiveness and rebound crankiness and tearfulness. Long-duration preparations have been developed in the past 15 years to overcome the need for multiple daily MPH doses, and these preparations are now the mainstay of practice.

In clinical practice, IR-MPH tablets are often used to provide a boost in the morning for certain long-duration forms, such as OROS-MPH, or to smooth withdrawal in the late afternoon. When used as the main ADHD treatment, IR-MPH should be administered before school, at lunch, and at home prior to homework (Greenhill et al., 1996). IR-MPH should be initiated at low doses, 5 mg in the morning for children and 10 mg for adults, and increased every 3 days by adding a noontime and an afternoon dose until the three-times-daily schedule is achieved. Preschool children generally need a total daily dose of approximately 15 mg and school-aged children need about 30 mg daily (Greenhill et al., 1996). Although not FDA approved, some older children may require more than 60 mg/day.

Short- and long-duration MPH preparations demonstrate the same common adverse event profile during placebo-controlled RCTs. These include delay in sleep onset, appetite loss, weight decrease, headache, abdominal pain, and new-onset tics. Other adverse effects reported as infrequent are nausea, abdominal pain, dryness of the throat, dizziness, palpitations, headache, akathisia, dyskinesia, and drowsiness.

Rare, serious, and unexpected adverse events include angina, tachycardia, hypertension, visual hallucinations, auditory hallucinations, priapism, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme, and thrombocytopenic purpura. Also rare are tactile hallucinations, formication, phobias of insects, leucopenia, anemia, eosinophilia, transiently depressed mood, sudden unexpected death, and hair loss. Neuroleptic malignant syndrome has been reported very rarely and only when MPH is used in combination with drugs that are associated with neuroleptic malignant syndrome.

MPH interacts with a few medications, including MAO inhibitors (isocarboxazid, phenelzine, selegiline, and tranylcypromine), as well as antibiotics with MAO-inhibiting activity (linezolid), leading to blood pressure elevations and increase in MPH serum concentrations. For this reason, MAO-inhibiting medications are contraindicated in those taking stimulant medications. Furthermore, phenytoin, phenobarbital, tricyclic antidepressants, and warfarin increase the MPH serum concentrations. The effects of centrally acting antihypertensives (guanadrel, methyldopa, and clonidine) can be reduced by MPH. Neuroleptic malignant syndrome has been reported in patients treated with both venlafaxine and MPH.

Despite IR-MPH's effectiveness, its short, 3- to 5-hour duration of action means that a midday dose in school is necessary, which can expose children to peer ridicule. The short duration of action also requires administration by nonfamily members when children participate in after-school programs. Long-duration MPH preparations address these problems with a once-daily dosing formulation (Biederman, Lopez, Boellner, & Chandler, 2002; Greenhill, Findling, & Swanson, 2002; Greenhill et al., 2006b; McCracken et al., 2003; Pelham et al., 1999; Wolraich et al., 2001). An MPH transdermal patch (Findling et al., 2005) and an extended-release oral suspension of MPH (Wigal et al., 2103) have also been approved for the pediatric population. The long-duration MPH formulations differ in the number and shape of the MPH pulses released into the circulation. They include the older single-pulse MPH drugs, such as Ritalin SR and Metadate ER, and the newer dual-pulse beaded MPH products such as Metadate CD, Ritalin LA, Quillivant SR, and Focalin XR, as well as the complex release formulations, such as OROS-MPH (Concerta).

Single-pulse sustained-release, long-duration MPH formulations (Ritalin SR, Metadate ER) use a wax matrix to prolong delivery. They display a slower onset of action than IR-MPH, produce lower serum concentrations, and have up to an eight-hour duration of action (Birmaher, Greenhill, Cooper, Fried, & Maminski, 1989). Clinicians regard these as less effective in practice than the immediate-release or the dual-pulse, beaded MPH or OROS preparations. To compensate for reduced effectiveness and slow onset of action, the single-pulse drugs should be given twice daily or supplemented with an immediate-release tablet in the morning. Metadate ER and Methylin ER are referred to as "branded generics" because they are copies of Ritalin ER.

The beaded MPH products use an extended-release formulation with a bimodal release profile. In Ritalin LA, this is created using a proprietary Spheroidal Oral Drug Absorption System (SODAS) technology. MPH products using SODAS technology (Ritalin LA, Metadate CD, and Focalin XR) may help young children who have difficulty swallowing pills by allowing their bead content to be sprinkled on food. The capsule is opened, and contents—tiny medication spheres—can be sprinkled into a small amount of cold applesauce or pudding. The SODAS technology uses bead-filled capsules, mixtures of

immediate-release and enteric-coated delayed-release MPH beads (Metadate CD contains 30% IR-MPH beads and 70% delayed-release beads), providing a two-pulse release system that mimics the use of IR-MPH given in two doses 4 hours apart. Both Ritalin LA and Metadate CD 10-, 20-, 30-, and 40-mg capsules provide the same amount of MPH in a single dose as twice-daily IR-MPH dosages of 5, 10, 15, or 20 mg. Ritalin LA and Metadate CD given once daily exhibit a lower second peak concentration ($C_{max}2$), higher inter-peak minimum concentrations, and less peak-to-peak trough fluctuations in serum concentration of MPH than IR-MPH tablets administered 4 hours apart. This may be due to an earlier onset and more prolonged absorption of the delayed-release beads. The efficacy of Ritalin LA in the treatment of ADHD in children aged 6 to 14 meeting criteria for ADHD was established in one controlled trial in 2003 (Biederman et al., 2003).

Dexmethylphenidate hydrochloride (*d*-MPH, Focalin) is the *d*-threo-enantiomer of racemic MPH. The drug's plasma concentration increases rapidly after ingestion, reaching a maximum in the fasted state at about 1 to 1.5 hours postdose (Quinn et al., 2004; Wigal et al., 2004). Plasma *d*-MPH levels were comparable to those achieved following single racemic IR-MPH doses given as capsules in twice the total milligram amount. *d*-MPH (5, 10, or 20 mg/day total dose), racemic MPH (10, 20, or 40 mg/day total dose), and placebo, all administered twice daily, were compared in a multicenter, 4-week, parallel group study of 132 patients. Patients treated with *d*-MPH showed a statistically significant improvement in SNAP-IV teacher-rated symptom scores from baseline over patients who received placebo (Wigal et al., 2004).

Focalin XR (*d*-MPH) is an extended-release formulation of *d*-MPH with a bimodal release using the proprietary SODAS technology similar to that of Ritalin LA and Metadate CD. Each bead-filled Focalin XR capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads. Focalin XR 5-, 10-, and 20-mg capsules provide in a single dose the same amount of *d*-MPH as dosages of 2.5, 5, or 10 mg of Focalin IR given twice daily. After administration of Focalin XR, the first peak, on average, was 45% higher in females, even though pharmacokinetic *d*-MPH parameters were similar for males and females. Focalin XR's effectiveness was shown in a randomized, double-blind, placebo-controlled parallel-group study of 103 pediatric patients, aged 6 to 17. Using mean change scores from baseline on teacher-rated Conners ADHD/*DSM-IV* scales (CADS-T), the study reported significantly greater decreases in ADHD scores for youth on the active Focalin XR than on the placebo (Greenhill et al., 2006b). The medication effectiveness for adult ADHD was reported in a 5-week, randomized, double-blind, parallel-group, placebo-controlled study of 221 adults, aged 18 to 60, who met ADHD criteria on the *DSM-IV* Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS-IV). Signs and symptoms of ADHD were substantially reduced for adults on 20, 30, or 40 mg of Focalin XR than for those randomized to placebo (Chavez et al., 2009).

The OROS-MPH caplet (Concerta) uses an osmotic delivery system to produce ADHD symptom reduction for up to 12 hours (Swanson et al., 2004; Wolraich et al., 2001). The caplet is coated with IR-MPH for immediate action. The long-duration component is delivered by an osmotic pump (OROS) that gradually releases the drug over a ten-hour period, producing slightly ascending MPH serum concentrations. Taken once daily, it mimics the serum concentrations produced by taking IR-MPH three times daily, but with less plasma level variation (Modi, Wang, Noveck, & Gupta, 2000). Claims have been made that long-duration preparations using the beaded dual-pulse technology have greater efficacy than OROS-MPH for controlling ADHD symptoms in the early morning hours (Swanson et al., 2004). However, two double-blind, placebo-controlled RCTs have tested the efficacy and safety of OROS-MPH compared with IR-MPH for ADHD children (Swanson et al., 2003; Wolraich et al., 2001), and both found equal efficacy. Another multisite trial showed that OROS-MPH (Concerta) has similar efficacy to IR-MPH over placebo and significantly reduced ADHD symptoms in adolescents when the upper dose range was extended to 72 mg/day (Wilens et al., 2006). The results show that once-daily OROS-MPH dosing matches IR-MPH in the robust reductions of ADHD symptoms. Low placebo response rates are similar to the rates reported in the MTA Study. In addition, OROS-MPH has been demonstrated in a small study ($N = 6$) to have a longer duration for reducing ADHD-induced driving impairments in the evening than IR-MPH given three times daily (Cox et al., 2004).

Short-duration branded MPH chewable tablets or solutions have been formulated for young children who have difficulty swallowing pills or capsules. Methylin chewable tablets show peak plasma MPH concentrations in 1 to 2 hours (T_{max}), with a mean peak concentration (C_{max}) of 10 mg/mL after a 20-mg chewable tablet. High-fat meals delay the peak by one hour (1.5 hours, fasted, and 2.4 hours, fed), similar to what is seen with an IR-MPH tablet. Methylin chewable tablets are available in 2.5-, 5-, and 10-mg doses. The Methylin oral solution is available in strengths of 5 and 10 mg/5 mL. Quillivant XR is a long-acting racemic MPH solution using LiquiXR technology that enables the continuous release of MPH in an oral liquid form; it has been approved by the FDA for use in children and adults.

In the transdermal MPH preparation (Daytrana), MPH is steadily absorbed after application of the patch, but it does not reach peak concentration until 7 to 9 hours later, with no noticeable action for the first two hours. Chronic dosing with the patch results in higher peak MPH levels than for equivalent OROS-MPH doses, suggesting increased absorption. Duration of MPH action for a 9-hour wear period is about 11.5 hours. A double-blind, placebo-controlled, crossover study conducted in a laboratory classroom showed significantly lower ADHD symptom scores and higher math test ratings on active versus placebo patch for postdose hours 2 through 9 (McGough et al., 2006). Transdermal MPH (Daytrana) appears to be as effective as other long-duration MPH preparations, but adverse effects, such as anorexia, insomnia, and tics, occur more frequently with the patch, and mild skin reactions are common. An advantage of the transdermal formulation is that it can be removed early in patients who suffer from insomnia.

Amphetamines are manufactured in a monoisomer dextro formulation, as in DEX (Dexedrine, ProCentra, Vyvanse), or in racemic forms, with mixtures of salts of *d*- and *l*-amphetamine (Adderall or Adderall XR). The efficacy of these amphetamine products resembles that of the MPH products for controlling overactivity, inattention, and impulsivity in ADHD patients. Some children who have adverse events associated with MPH may respond without such problems when taking amphetamine products. Absorption is rapid, and the drug's plasma level peaks 3 hours after oral administration. All amphetamines are hepatically metabolized. Taking the medication with ascorbic acid or fruit juice acidifies the urine and decreases absorption of amphetamine, whereas alkalinizing agents such as sodium bicarbonate increase it (Vitiello, 2006). Effects of DEX can be seen within 1 hour of ingestion, and the duration of action lasts up to 6 hours, somewhat longer than that of MPH. Nevertheless, twice-daily administration is needed to extend the effectiveness of the IR preparation throughout the school day.

Adderall and Adderall XR are amphetamine salt mixtures (MAS). Adderall XR is a dual-pulse capsule preparation that includes both immediate- and extended-release beads. There is no RCT evidence that MAS offer any advantage over MPH or DEX, but some patients can respond to one and not to another.

Lisdexamfetamine dimesylate (Vyvanse) is a pro-drug preparation that has been FDA approved for treatment of children and adolescents (6 to 17 years) and for adults. It is converted to DEX in the bloodstream upon cleavage of the covalently bonded lysine portion of the molecule. It was developed with the intention of creating a longer-lasting and less easily abused version of DEX. Due to the requirement of cleavage of lysine in the bloodstream, the medication may have a somewhat lower abuse and overdose liability if injected or inhaled. Also, requirement of the conversion into DEX via enzymes in the red blood cells increases its duration of action, regardless of the route of ingestion (Mattingly, 2010). It is available in 20-, 30-, 40-, 50-, 60-, and 70-mg capsules. The starting dose is 30 mg once daily in the morning. The dose can be raised in increments of 10 to 20 mg/day once per week, and the maximum dose is 70 mg/day.

Lisdexamfetamine dimesylate in doses between 30 and 70 mg for 3 to 4 weeks was shown to be both efficacious and well tolerated in two double blind, randomized, placebo-controlled clinical trials of children (6 to 12 years) with ADHD. The first was a phase II, double blind, placebo- and active-controlled crossover of 52 children, comparing the efficacy and safety of lisdexamfetamine dimesylate (30, 50, or 70 mg), with extended-release MAS (MAS XR) (10, 20, or 30 mg) included as a reference arm (Biederman et al., 2007a). There were significant reductions in ADHD symptoms as well as global clinical improvement in both the lisdexamphetamine and the MAS XR arms when compared to placebo. The second was a phase III, double-blind, placebo-controlled parallel study of 290 children with ADHD, randomly assigned to receive lisdexamfetamine dimesylate (30, 50, or 70 mg) with forced dose titration or to receive

placebo (Biederman et al., 2007b). As early as the first week, there were significant improvements on several parent- and teacher-validated efficacy measures with all doses of lisdexamphetamine as compared to placebo. The primary outcome measure was improvement in ADHD-RS-IV scores. Adverse effects occurred in at least 5% of the children assigned to active medication at a rate of twice that of the placebo group. The most common adverse effects included upper abdominal pain, decreased appetite, nausea, vomiting, decreased weight, dry mouth, irritability, and insomnia. In addition, children taking lisdexamphetamine had small but statistically significant increases in blood pressure and pulse.

In addition, lisdexamphetamine has been shown to be efficacious for both the short-term and maintenance treatment of adults with ADHD. Evidence for the short-term treatment came from two double-blind, randomized, placebo-controlled trials including a total of 562 adults (aged 18 to 55 years) with ADHD. In the first study, 420 adults with ADHD were randomized in a parallel design to receive 30, 50, or 70 mg lisdexamphetamine or placebo for a total of 4 weeks (Faraone et al., 2012). All lisdexamphetamine dose groups were found to be superior to placebo in the primary outcome measure (change in total score from baseline to endpoint in the investigator ratings on the ADHD-RS-IV). The second short-term study was a multicenter, randomized, placebo-controlled, crossover, modified study of lisdexamphetamine conducted in a setting designed to simulate a workplace environment in 142 adults with ADHD (Wigal et al., 2010). The study began with a 4-week open-label, dose-optimization phase with lisdexamphetamine (30, 50, or 70 mg/day in the morning). Subsequently, patients were randomized to one of two treatment sequences: lisdexamphetamine (optimized dose) followed by placebo, or placebo followed by lisdexamphetamine, each for one week. The primary outcome measure, the Permanent Product Measure of Performance (PERMP), a skill-adjusted math test that measures attention in ADHD, was assessed at the end of each week. Lisdexamphetamine treatment compared to placebo resulted in a statistically significant improvement in attention across all postdose time points, as measured by average PERMP total scores over the course of the day, as well as scores at each time point measured (up to 14 hours after the morning dose). Based on a 2012 study by Brams and colleagues, lisdexamphetamine has also been shown to be an effective maintenance treatment for adults with ADHD. This phase IV, double-blind, multicenter, placebo-controlled, randomized withdrawal design study assessed the maintenance of efficacy and safety in 123 adults with ADHD. Prior to enrollment, patients were required to have documented long-term treatment with lisdexamphetamine (30, 50, or 70 mg/day) for at least 6 months and have demonstrated treatment response. Subsequently, for 6 weeks, patients either were randomized to continue treatment or were switched to placebo. At the study endpoint, 8.9% of adults taking lisdexamphetamine and 75% taking placebo showed symptom relapse; most showed relapse after 1 and 2 weeks of the randomized withdrawal phase (Brams et al., 2012).

INITIATING STIMULANT DRUG TREATMENT IN PRACTICE

Predicting the individual drug response in ADHD children is difficult. While pretreatment patient characteristics (i.e., young age, low rates of anxiety, low severity of disorder, and high IQ) may predict a good response to MPH on global rating scales (Buitelaar, Van der Gaag, Swaab-Barneveld, & Kuiper, 1995), most research shows that neurological, physiological, or psychological measures of functioning have not been identified as reliable predictors of response to psychostimulants (Pelham & Milich, 1991; Zametkin & Rapoport, 1987). Once a child responds, there is no universally agreed-upon criterion for how much the symptoms must change before the clinician stops increasing the dose. Furthermore, there is no standard for the outcome measure. For example, should global ratings alone be used, or should they be combined with more "objective" academic measures such as percentage correct or percentage completed lists of math problems? Some have advocated a 25% reduction of ADHD symptoms, whereas others have suggested that the dose should continue to be adjusted until the child's behavior and classroom performance are normalized.

The concept of normalization has helped standardize the definition of a categorical responder across domains and across studies. Studies now determine whether the improvement from treatment is clinically meaningful using normal classroom controls, instead of just being statistically significant. Treatment was noted to remove differences

between ADHD children and nonreferred classmates on measures of activity and attention (Abikoff & Gittelman, 1985), but not for positive peer nominations (Whalen et al., 1989). Further advances occurred when investigators used statistically derived definitions of clinically meaningful change during psychotherapeutic treatment (Jacobson & Truax, 1991). Rapport and colleagues (1994) used this technique to calculate reliable change and normalization on the Abbreviated Conners Teacher Rating Scale (ACTRS) using national norms. They determined that a child would be normalized when his or her ACTRS score fell closer to the mean of the normal population than to the mean of the ADHD population. Using this technique in a controlled trial of four MPH doses in ADHD children, they found that MPH normalized behavior and, to a lesser extent, academics (94% vs. 53%). Similarly, DuPaul and colleagues (DuPaul & Rapport, 1993) found that MPH normalized behavior for all ADHD children treated, but only 75% of the ADHD children normalized for academics. In another study, the same group (DuPaul et al., 1994) reported that normalization in behavior and academics occurred less often when ADHD subjects were comorbid for high levels of internalizing disorders. Swanson applied this approach to the cumulative-distribution curves of the SNAP-IV parent and teacher ratings at the end of the MTA Study and found that 88% of classroom controls, 65% of ADHD children treated with combined treatment, and 55% of ADHD children treated with MTA medication strategies had mean symptom scores of 1 or less, equivalent to a "normal" response on those scales.

NEUROIMAGING STUDIES

To date, brain imaging has not been able to completely explain the mechanism by which stimulants reduce the level of ADHD symptoms. Although some studies in ADHD adults using positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose show that stimulants lead to increased brain glucose metabolism in the striatal and frontal regions (Ernst & Zametkin, 1995), others (Matochik et al., 1993, 1994) could not find a change in glucose metabolism during acute and chronic stimulant treatment.

Structural magnetic resonance imaging (MRI) studies of children with ADHD have suggested volumetric disturbances in multiple cortical and subcortical regions (Durston, 2003). For example, in a study of 57 boys with ADHD and 55 matched healthy controls, total brain volumes were found to be 4.7% smaller in affected relative to unaffected boys (Castellanos et al., 1996). Analogous findings have been reported in girls with ADHD (Castellanos et al., 2001), and these findings were replicated in a sample of 152 boys and girls with ADHD (Castellanos et al., 2002). Likewise, a morphometric study examining the sizes and surface contours of the basal ganglia in 47 children with ADHD found volumetric reductions in the putamen, as well as abnormal surface morphology in other basal ganglia nuclei (Sobel et al., 2010). Earlier studies on the basal ganglia of children with ADHD have been inconsistent, with some research suggesting volumetric reductions in the left caudate (Filipek et al., 1997) and other research suggesting reductions in the size of the right, but not left, caudate (Castellanos et al., 1994). Interestingly, studies that have compared children with ADHD treated with stimulants versus untreated children suggest that stimulants may reduce, or normalize, some of the detected volumetric abnormalities (Castellanos et al., 2002; Sobel et al., 2010). These studies, however, have been cross-sectional in nature and the findings should be interpreted with caution. Replication with longitudinal, placebo-controlled designs is needed to better establish stimulant-induced change in brain structure.

Studies of ADHD using functional neuroimaging, which assesses neural activity in the context of specific cognitive operations, have focused largely on deficits in inhibitory and cognitive control, employing tasks that assess children's ability to restrain urges. Several functional MRI (fMRI) studies using tasks associated with cognitive control such as the Go No-Go, Stroop, or Stop-Signal Task have demonstrated that children with ADHD have altered task-related activations in frontostriatal circuits that encompass the dorsolateral prefrontal cortex, basal ganglia, and thalamus and are thought to underlie disturbances in impulsivity (Durston, 2003; Marsh, Maia, & Peterson, 2009; Paloyelis et al., 2007). There have, however, been inconsistencies in the direction of these abnormalities, with some studies suggesting hyperactivation of frontostriatal circuits in ADHD (Schulz et al., 2004, 2005; Pliszka et al., 2006b) and others suggesting hypoactivation of these circuits (Booth et al., 2005; Rubia et al.,

1999). Differences in the age ranges of the samples may have had important effects on the detected patterns of neural activity, underscoring the importance of longitudinal study designs.

The effects of stimulants on fMRI activations have been examined in ADHD by scanning patients in medicated and unmedicated states (Posner et al., 2011a, 2011b), comparing the effects of treatment with either placebo or stimulant employing randomized double-blind designs (Bush et al., 2008; Cubillo et al., 2012), and by comparing medication-naïve children to those who have received long-term stimulant treatment (Pliszka et al., 2006b). Taken together, these studies suggest that stimulants may normalize activation within the frontostriatal circuits, including the right inferior frontal and midcingulate cortices (Bush et al., 2008, Cubillo et al., 2012), as well as the striatum (Vaidya et al., 2005), although it remains unclear whether this normalization mediates symptom improvement. Additional fMRI studies have examined the effects of stimulants on neural circuits underlying emotional regulation and processing and suggest that stimulants may have a direct salutary effect on these circuits, offering a potential mechanistic explanation for stimulant-induced reductions in emotional lability (Posner, 2011a, 2011b).

Dopamine transporter (DAT) blockade is regarded as the putative mechanism for psychostimulants in the human central nervous system. For instance, MPH has high affinity for the DAT. PET scan data in adult substance abusers show that [^{11}C] MPH concentration is maximal in striatum, an area rich in DA terminals where DAT resides (Volkow et al., 1995). These scans reveal a significant difference in the pharmacokinetics of [^{11}C] MPH and [^{11}C] cocaine. Although both drugs display rapid uptake into striatum, MPH is more slowly cleared from brain. The authors interpret the slow reversal of binding to DAT to mean that MPH is not as reinforcing as cocaine and therefore is less likely to lead to self-administration. Therapeutic oral MPH doses significantly increase extracellular DA in the human brain. Volkow and colleagues (2001) have speculated that "Because DA decreases background firing rates and increases signal-to-noise in target neurons, the amplification of weak DA signals in subjects with ADHD by MPH would enhance task-specific signaling, improving attention and decreasing distractibility. (p. 3)"

ADVERSE EVENTS WITH STIMULANTS

Common adverse events frequently reported during stimulant use include delay of sleep onset, headache, appetite decrease, and weight loss. Infrequently observed adverse events include emotional lability and tics. All stimulant products carry a warning in the package insert that they should be used with care in patients with a history of drug dependence or alcoholism.

The most common adverse events associated with stimulant discontinuation in controlled trials included twitching (e.g., motor and vocal tics), anorexia, insomnia, and tachycardia, with reported incidence rates of approximately 1%. Motor or vocal tics have been reported in as many as 1% of children taking MPH (Ickowicz, Tannock, Fulford, Purvis, & Schachar, 1992). Nonetheless, a controlled MPH trial in ADHD children with chronic tic disorder (Gadow et al., 1995) reported significant improvement in ADHD symptoms for all subjects without consistent worsening or increase in tic frequency. However, the total daily MPH doses did not exceed 20 mg/day. These low doses and the short 8-week study do not resemble the higher doses or longer treatment duration found in clinical practice, where tics may appear after several months of MPH administration. More recently, a 2009 meta-analysis of 447 subjects with ADHD and comorbid tic disorders concluded that stimulants do not seem to worsen tics, with the exception of supratherapeutic doses of amphetamine (Bloch, Panza, Landeros-Weisenberger, & Leckman, 2009). The practitioner should keep in mind that transient tics are very common in children (8% to 20%) between the ages of 6 and 10. Furthermore, in a population with a tic disorder, ADHD is found in approximately 50% of patients. Although there is not a large increase in new-onset tics in children taking stimulants, there is the possibility that these medications may uncover a predisposition for tics. Although the clinical literature has held that MPH lowers the seizure threshold, MPH treatment of ADHD patients with seizures is not associated with an increase in seizure frequency (Klein, 1995).

Several clinical conditions have been worsened by stimulant treatment, including florid psychosis, mania, concurrent substance abuse, Tourette syndrome, and eating disorders. More recently, preexisting structural cardiac lesions and hypertensive states

were added as contraindications for using stimulants to treat ADHD.

Drug response may be altered by comorbid anxiety. Stimulant responsiveness and rates of side effects were originally thought to be affected by the presence of comorbid anxiety symptoms. Pliszka (1989) used MPH (0.25 to 0.4 mg/kg and 0.45 to 0.70 mg/kg) and placebo to treat ADHD in 43 subjects for 4 weeks. The 22 ADHD subjects with comorbid anxiety showed less efficacy when active stimulant treatment was compared with placebo, as judged by teachers' global ratings, with no increase in side effects. This might be explained by strong placebo response in this group. Tannock, Ickowicz, and Schachar (1995a) reported that ADHD children, some with (N = 18) and some without (N = 22) comorbid anxiety symptoms, treated in a double-blind, randomized, crossover design with three MPH doses (0.3, 0.6, and 0.9 mg/kg), showed equal decreases in motor activity; however, children comorbid for anxiety had an enhanced risk for tics and dysphoria and less improvement in memory. The group with comorbid anxiety also did more poorly on a serial addition task and had a differential heart rate response to MPH. DuPaul, Barkley, and McMurray (1994) found that 40 children with ADHD and comorbid anxiety were less likely to respond to MPH and showed more side effects for three doses of MPH (5, 10, and 15 mg). The study did not collect ratings for anxiety symptoms, so the direct effect of MPH on such symptoms was not recorded.

More recent data suggest that comorbid anxiety neither decreases the efficacy nor increases the side effects of psychostimulants. A controlled study (Gadow et al., 1995) that tested the MPH effects in children with ADHD and anxiety found equally good response in those with and without comorbid anxiety disorders. Using a flexible clinically appropriate titration trial, Diamond and colleagues (1999) found no difference in short-term outcome or side effects in children with or without anxiety, implying that a method variance may, in part, account for conflicting results in these studies. Analyses of the MTA Study by Arnold and colleagues (1997) suggested that there was no adverse effect of parent-reported child anxiety on medication efficacy for core ADHD symptoms or other outcomes. These divergent data leave open the question of whether comorbid anxiety symptoms predict poor response to stimulant treatment.

Growth Slowdown During Stimulant Treatment

Growth slowdown is another psychostimulant adverse reaction. Psychostimulant-induced reductions in growth velocity have been the most consistently researched long-term side effect (Greenhill, 1984). Even with the many studies in this area (Greenhill, 1981), a myriad of methodologic difficulties prevents an easy interpretation. Few studies employ the optimal controls needed, which include untreated children with ADHD, a psychiatric control group, and an ADHD group treated with a class of medications other than stimulants. Studies differ in quality of compliance measures, whether the children are off stimulants on weekends, and whether the stimulants are used through the summer. One large controlled study (Gittelman-Klein et al., 1988) reported reductions in growth rate among a subgroup of children taking stimulants but noted that growth resumed immediately after treatment was interrupted (Safer et al., 1975). Safer and Allen (Safer et al., 1972, 1975; Safer & Allen, 1973) first reported that treatment for two or more years with MPH and DEX could produce decrements in weight velocity on age-adjusted growth rate charts; stopping the medication produced a quick return to baseline growth velocities. DEX, with a half-life two to three times that of MPH, produces more sustained effects than MPH on weight velocity, as well as suppressing mean sleep-related prolactin concentrations (Greenhill, 1981). In MPH-treated ADHD children followed for 2 to 4 years, dose-related decreases in weight velocity were seen (Gittelman-Klein et al., 1988; Satterfield et al., 1979), with some tolerance of the suppressive effect developing in the second year. Hechtman and colleagues (1984) reported growth slowdown in untreated ADHD children, suggesting that there may be differential growth associated with the ADHD disorder itself. Spencer and colleagues (1996b) also detected similar different growth rates for ADHD children that could be associated with the disorder itself and not with stimulant treatment alone.

More recently, in the MTA Study, growth slowing for height and weight was reported for 288 children aged 7 to 10 with ADHD, combined subtype, treated with MPH at mean doses of 30 mg/kg per day (Swanson et al., 2002). School-age children grew 1.0 cm less per year and gained 2.5 kg less than

predicted from CDC growth charts. Similar effects were observed for preschool children in the NIMH PATS (Swanson et al., 2006), who grew 1.5 cm less and gained 2.5 kg less than predicted by CDC growth norms while treated with mean MPH doses of 14 mg/kg per day. Two major reviews (Faraone et al., 2008; Poulton, 2005) concluded that stimulant treatment most likely slows height acquisition in children, at least during the first 1 to 3 years of treatment. Patients randomized to the stimulant arm in the MTA Study showed significantly less height acquisition during the first two years compared to patients in the nonstimulant arms. Interestingly, when youth with ADHD entered the MTA Study or the PATS, they were typically heaver and taller than average at the start of treatment. Thus, clinicians may not observe growth slowdown as often as predicted because the ADHD-treated children do not slow down in height acquisition enough to become shorter than average.

The actual mechanism for any growth slowdown caused by psychostimulants is unknown. Early theories attributed the drug's putative growth-suppressant action on its effects on growth hormone or prolactin, but research studies on 13 children treated for 18 months with 0.8 mg/kg per day of DEX (Greenhill et al., 1981) and on 9 children treated for 12 months with 1.2 mg/kg per day of MPH (Greenhill et al., 1984) failed to demonstrate a consistent change in growth hormone release. The most parsimonious explanation is appetite suppression, leading to reduced caloric intake. No study, however, has collected the standardized diet diaries necessary to track calories consumed by ADHD children on psychostimulants (Greenhill et al., 1981). There is also evidence that even if height acquisition is reduced during the first year of stimulant treatment, these effects attenuate after that time (Faraone et al., 2008). Pliszka and colleagues (2006a) found that amphetamine affected the rate of weight acquisition more than MPH, but neither had significant effects on the rate of height acquisition. The AACAP Work Group on Quality Issues Guidelines (2007) for ADHD recommends that no change in treatment should occur until the patient has a change in height or weight percentile that crosses two percentile lines on the CDC chart. If this happens, the clinician can reduce the dose, switch to another ADHD medication, or temporarily stop stimulant treatment.

Rare, Serious Adverse Events

The package insert for all psychostimulants includes a black box warning concerning sudden death that may be associated with preexisting cardiac abnormalities or other serious heart problems. This is a rare adverse event. For adults, the warning includes sudden death and also extends to stroke and myocardial infarction. In addition, adults are warned that they should be cautious taking stimulants if they have preexisting hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia. Those with preexisting psychotic and bipolar psychiatric illness are cautioned against taking stimulants.

These concerns arose from a series of reviews conducted by the FDA of cardiovascular and psychiatric adverse events associated with use of approved stimulant medications. On June 30, 2005, the agency began this review by examining the passive surveillance reports concerning treatment with OROS-MPH (Concerta) (http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4152s2_06_McCune.pdf). The review uncovered 135 adverse events, including 36 psychiatric adverse events and 20 cardiovascular events. In particular, the reports documented 12 instances of tactile and visual hallucinations (classified under "psychosis") on OROS-MPH, the same clinical phenomena seen in cases of delirium. These OROS-MPH adverse event reports represent 135 per 1.3 million cases and thus seem to be rare events.

Most worrisome were the data that revealed 20 cases of sudden unexpected death with amphetamine or DEX (14 children, 6 adults) and 18 cases with MPH (14 children, 4 adults) (Villalaba, 2006). Based on U.S. postmarketing reports of sudden death, Health Canada suspended the sale of Adderall XR in February 2006. Of the fourteen cases of sudden cardiac death in children taking amphetamine or DEX, six had documented structural cardiovascular abnormalities or other predisposing factors for sudden death on autopsy (Villalaba, 2006). Data from the FDA's Adverse Event Reporting System estimated that the rate of sudden death in children being treated for ADHD during the exposure period January 1, 1992, to December 31, 2004, was 0.2/100,000 patient-years for MPH and 0.5/100,000 patient-years for amphetamine (Villalaba, 2006). Notably, the rate of sudden death in the general pediatric population has been estimated at 1.3 to 8.5/100,000 patient-years, whereas the rate of sudden death among those with a history of

congenital heart disease can be as high as 6% by age 20 (Liberthson, 1996). Therefore, the rate of sudden death in children taking stimulants for ADHD does not appear to exceed the rate of sudden death in the general population (AACAP, 2007).

In March 2006, the FDA's Pediatric Advisory Committee voted unanimously against adding a black box warning for all patients taking stimulants. Instead, the black box warning was targeted to specific high-risk children, such as those with structural heart defects, cardiomyopathy, or an arrhythmia. In 2011, Cooper and colleagues conducted a large retrospective cohort study with over 1 million children and young adults from four separate health plans and found no evidence that current use of an ADHD drug was associated with an increased risk of serious cardiovascular events (Cooper et al., 2011).

In summary, serious unexpected cardiac adverse events associated with stimulants have been known for years and are extremely rare. The rates of cardiac adverse effects are too low to prove a causal association with stimulants in patients with no history of previous heart disease. Routine electrocardiograms and echocardiograms are not indicated before starting stimulants in a patient who has an unremarkable history and physical examination. The physician prescribing stimulants should first ask patients and their families if they have a history of structural heart disease and whether they have consulted previously with a cardiologist. Known cardiac problems that raise a caution about using stimulants include a history of tetralogy of Fallot, cardiac artery abnormalities, and obstructive subaortic stenosis. Clinicians should be alert if the patient has hypertension or complains of syncope, arrhythmias, or chest pain, as these symptoms may indicate hypertrophic cardiomyopathy, which has been associated with sudden unexpected death (AACAP, 2007).

Stimulant Treatment for Children with ADHD and Subsequent Substance Use Disorder

Even though psychostimulants are the most widely researched and clinically effective treatment for childhood ADHD, controversy remains regarding their classification as drugs of abuse, which creates concern about their being administered to young children to treat a condition that has no readily available laboratory test validating the diagnosis. There is also the prominent question of whether children who take stimulants are at an increased risk for later substance use disorders. This subject can be challenging to study, as ADHD itself (particularly when comorbid with CD) is a risk factor for substance abuse. Children with ADHD are significantly more likely to develop substance use disorders in adolescence and adulthood than children without ADHD (Charach et al., 2011). A meta-analysis from 2011 demonstrated that children with ADHD have a 1.5-fold increased risk for developing any substance use disorder and a nearly three times greater risk for developing nicotine dependence (Lee et al., 2011). Nonetheless, there are data from several early long-term clinical studies that suggested that treatment with MPH during childhood reduces the risk of later addiction and substance abuse, including alcohol, nicotine, and drug abuse (Biederman et al., 1999). Several subsequent studies showed no such correlation (Wilens et al., 2003). A 10-year prospective follow-up study of 140 boys (ages 6 to 17 years) with ADHD showed no evidence that stimulant treatment increases or decreases the risk for subsequent substance use disorders in children and adolescents when they reach young adulthood (Biederman et al., 2008a). There was also no significant association between age at stimulant treatment onset and subsequent substance use disorders or any association between the duration of stimulant treatment and subsequent substance abuse disorders. Another recent meta-analysis of 15 long-term studies followed 2,565 children with ADHD from childhood into adolescence and young adulthood. Results suggested comparable outcomes between children with and without medication treatment history for any substance use disorder outcome across all substance types. These results provide an important update and suggest that ADHD treatment with stimulant medication neither protects against nor increases the risk of later substance use disorders (Humphreys et al., 2013).

NONSTIMULANT MEDICATION TREATMENTS FOR ADHD

Because of the controversy surrounding the use of scheduled drugs in children, clinicians and parents may prefer nonstimulant medications for ADHD treatment (Table 4.3). Besides the controversy, other problems face the family using stimulants for ADHD.

TABLE 4.3 Nonstimulant Drugs with FDA Indication for ADHD

Medication (Brand Name)	*Available Dose of Preparation*	*Starting Dose/ Maximum Dose*	*Indicated Age (Years) for Psychiatric Use*
Atomoxetine (*Strattera*) † *	10-, 18-, 25-, 40-, 60-, 80-, 100-mg tabs	**<70 kg**: 0.5 mg/kg/1.2 mg/kg **>70 kg**: 40 mg/day/100 mg/day (Maintain initial dose for minimum of 7 days prior to upward dose titration)	6+
Bupropion (*Wellbutrin; Wellbutrin SR, Wellbutrin XL*) †	*Wellbutrin*: 75-, 100-mg tabs *Wellbutrin SR*: 100-, 150-, 200-mg tabs *Wellbutrin XL*: 150-, 300-mg tabs	*Wellbutrin*: 100 mg b.i.d./150 mg/dose up to 450 mg/day *Wellbutrin SR*: 100 mg AM/400 mg/day *Wellbutrin XL*: 150 mg AM/450 mg/day	18+ (off-label for pediatric ADHD)
Clonidine (*Catapres*)		**27–40.5 kg**: 0.05 mg qhs/0.05 mg/dose up to 0.2 mg/day **40.5–45 kg**: 0.05 mg qhs/0.1 mg/dose up to 0.3 mg/day **>45 kg**: 0.1 mg qhs/0.1 mg/dose up to 0.4 mg/day	18+ (off-label for pediatric ADHD)
Guanfacine Immediate Release (*Tenex*)		**27–40.5 kg**: 0.5 mg qhs/0.5 mg/dose up to 2 mg/day **40.5–45 kg**: 0.5 mg qhs/1 mg/dose up to 3 mg/day **>45 kg**: 1 mg qhs/1 mg/dose up to 4 mg/day	18+ (off-label for pediatric ADHD)
Clonidine Extended Release (*Kapvay*) †		0.1 mg qhs/0.4 mg/day (divide doses >0.1 mg/day)	6+
0.1-, 0.2-, 0.3-mg tabs		1 mg/day (morning or evening)/4 mg/day	6+

†Must be swallowed (not crushed or chewed)

*FDA approved for treating adult ADHD

Short-acting stimulants require cooperation from the school personnel for midday dosing, and this may not always be possible. Stimulants, which cause insomnia, cannot be given too late in the day. MPH's attention-enhancing effects, which last only 3 to 4 hours, are often needed in the late evening to help school-age children with their homework but may result in delayed sleep onset and insomnia. Adverse effects, including weight loss, headaches, insomnia, and tics, can occur. March, Conners, Erhardt, and Johnson (1994) suggested that a nonstimulant may be used when there is an unsatisfactory response to two different stimulants; this recommendation is in congruence with the studies of Elia and colleagues (1991). Other ADHD treatment parameters, including the Texas Children's Medication Algorithm Program, recommend the use of nonstimulants when stimulants cannot be used because of inadequate response, unwanted side effects, or parental preference (Pliszka et al., 2000; Pliszka et al., 2006a).

ATX (Strattera) is a potent selective norepinephrine reuptake inhibitor and was approved in the United States in November 2002 for the treatment of ADHD in children (6 years and older), in adolescents, and in adults. Results from premarketing randomized placebo-controlled trials demonstrated effect sizes between 0.6 and 0.8 (Kelsey et al., 2004; Michelson et al., 2001, 2002; Spencer et al., 2002). A large parallel-group, placebo-controlled, double-blind study compared the acute treatment response of ATX versus MPH in the treatment of ADHD in children and adolescents. In this study, 561 children and adolescents (6 to 16 years) with ADHD were randomized to receive ATX (0.8 to 1.8 mg/kg per day), OROS-MPH (18 to 54 mg/day), or placebo for six weeks. The response rates for both ATX (45%)

and MPH (56%) were markedly superior to those for placebo (24%), but the response to OROS-MPH was superior to that for ATX (Newcorn et al., 2008). Following 6 weeks of treatment, patients treated with MPH were switched to ATX under double-blind conditions. Approximately one third of the patients responded preferentially to either ATX or to MPH. About half responded to both treatments, and 22% did not respond to either treatment. This finding suggests that a subgroup of patients may derive greater benefit from one or the other treatment. This may be attributable to differential sensitivity to the pharmacological mechanisms and individual metabolic and pharmacokinetic responses (Newcorn et al., 2008). There is also evidence for the efficacy of ATX for the maintenance treatment of ADHD in patients who responded to initial treatment with ATX (Michelson et al., 2004).

ATX's value as a treatment is for patients who have not responded to or cannot tolerate stimulants, or for those who do not want treatment with a schedule II stimulant ("Atomoxetine for ADHD," 2003). ATX is neither a controlled substance nor a stimulant. It is rapidly absorbed, with peak serum concentrations occurring in 1 hour without food and 3 hours with food. The drug undergoes hepatic metabolism with CYP2D6 isozyme and then is glucuronidated and excreted in urine. Plasma elimination half-life averages 5 hours for most patients, although 5% to 10% of patients have a polymorphism for the allele that codes for CYP2D6 and show ATX half-life as long as 24 hours. The pharmacodynamics differs from the pharmacokinetics in that the duration of action in reducing ADHD symptoms lasts much longer than the pharmacokinetic half-life, so once-daily dosing can manage ADHD symptoms. ATX is usually administered as a single morning dose but can, if necessary, be given in the evening, whereas stimulants cannot. ATX dosage for children and adolescents is weight-dependent. The recommended starting dose for youth weighing 70 kg or less is 0.5 mg/kg per day divided into two equal doses the first week and increased after 1 week to a target dose of 1.2 mg/kg per day to limit adverse events. In patients weighing more than 50 kg, treatment can be initiated with 18 mg during the first week, and those weighing more than 70 kg can start with 40 mg. Concurrent administration of CYP2D6 inhibitors, such as paroxetine, fluoxetine, metoprolol, or propranolol, requires lower dosages, as ATX levels can be increased three- to fourfold. ATX and MAO inhibitors should not be used together or within 2 weeks of each other. Dry mouth, somnolence, nausea, decreased appetite, and vomiting have occurred in children on ATX, particularly when the dose is increased from initial to top levels within three days. Slow metabolizers displayed higher rates of decreased appetite. Contraindications and relative contraindications include congenital or acquired long QT syndrome, a family history of prolonged QT interval, cerebral seizures or a history of seizures, and hepatic dysfunction.

Two warnings have been added to the ATX package insert instructions. The first warning was added on December 17, 2004, based on three spontaneously reported cases of reversible drug-induced liver injury that were deemed probably related to ATX. ATX should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted (Bangs et al., 2008). The second warning was added in September 2005. Lilly Pharmaceuticals reported that 5 of 1,800 youth in ATX trials spontaneously reported suicidal ideation, whereas none randomized to placebo made such reports. The FDA required that ATX's label carry a black-box warning about its possible association with suicidality. A 2008 meta-analysis, including 14 pediatric clinical trials, demonstrated that the frequency of suicidal ideation was greater among ATX-treated (0.37%) than among placebo-treated patients (0%); however, no patients in these trials committed suicide. It is noteworthy that both warnings are based on spontaneous reports, not systematically elicited adverse events.

Bupropion, an antidepressant with noradrenergic activity, has been reported to be effective for some ADHD symptoms in placebo-controlled trials (Casat et al.,1989; Clay et al., 1988; Simeon et al., 1986). Barrickman and colleagues (1995) concluded that bupropion was equivalent to MPH in the treatment of 15 children with ADHD, who had equal improvements for both medications on the Clinical Global Impression scale, Conners teacher and parent ratings, the Continuous Performance Test, and ratings of anxiety and depression. The study shows an order effect, which suggests a carryover from one drug condition to the next. Also, subjects were not placed on placebo in the crossover, so the study is not placebo controlled. The multisite, double-blind, placebo-controlled trial of bupropion revealed that teachers could detect a reduction of ADHD symptoms at a significant level but parents could not (Conners et al., 1996). This

suggests that bupropion is a second-line agent for ADHD treatment.

Clonidine and guanfacine were initially developed and used clinically as centrally active antihypertensive agents, which exert their antihypertensive activity by decreasing sympathetic tone in the central nervous system and reducing vascular resistance. Clonidine is a central α_2-adrenergic pre- and post- synaptic receptor agonist with high affinity at each of the three postsynaptic α_2-receptor subtypes (α_2A, α_2B, α_2C), whereas guanfacine is selective for the α_2A-receptor subtype (15-60 times more selective for the α_2A than for α_2B and α_2C) (Stahl, 2013). In clinical practice, both clonidine and guanfacine have been used to treat ADHD, both alone and with psychostimulants, especially in patients unable to tolerate pychostimulants or in those who present clinically with comorbid disorders such as Tourette syndrome/tic disorders, impulsive aggression, or insomnia (Sallee, 2010; Scahill et al., 1999).

Only the extended-release formulations of clonidine (Kapvay) and guanfacine (Intuniv) are FDA approved as monotherapy or adjuvant therapy for children and adolescents (aged 6–17 years) with ADHD. Neither medication has an FDA indication for the treatment of adults. A meta-analysis of 11 small double-blind and open-label studies (fewer than 50 subjects) that reviewed the effects of treatment with immediate-release clonidine on symptoms of ADHD alone, or ADHD comorbid with developmental, conduct, or tic disorders, determined a moderate overall effect size of 0.58 ± 1.6 (Connor et al., 1999). The efficacy of extended-release clonidine monotherapy was evaluated in an 8-week double-blind placebo-controlled forced dose titration study in children and adolescents (aged 6 to 17 years) with ADHD. Subjects in the active arm were randomized to receive either 0.2 or 0.4 mg/day. Subjects were started on 0.1 mg at bedtime, and their doses were increased by 0.1 mg/week until the target dose (0.2 or 0.4 mg/day) was reached. Improvement from baseline in ADHD-RS-IV total score (primary efficacy variable) was significantly greater in both clonidine groups versus placebo, with an effect size of 0.71 for 0.2 mg/day and 0.76 for 0.4 mg/day (Jain et al., 2011). The significant limitation of this fixed-dose protocol was the high discontinuation rate in all treatment arms, particularly in the 0.4-mg/day group. Nonetheless, there was ample power to demonstrate a robust treatment effect (change from baseline of 15 to 16 points on the ADHD-RS-IV) (Sallee et al., 2013).

There are only limited data available for immediate-release guanfacine, including several small studies showing improvement in both parent and teacher ADHD rating scales (summarized in Sallee et al., 2013). Two short-term (8- and 9-week) studies showed both the efficacy and the safety of using extended-release guanfacine as monotherapy for ADHD. Both were multicenter, randomized, fixed-dose, placebo-controlled trials in children and adolescents (aged 6 to 17 years) (Biederman et al., 2008b; Sallee et al., 2009b). Both studies used fixed-dose protocols and demonstrated a significant reduction in the ADHD-RS-IV total score for the entire study population, except for the 13- to 17-year-old subgroups. Effect sizes ranged from 0.43 to 0.86, and there was a correlation between efficacy and dose strength (Biederman et al.: 0.64 [2 mg/day] and 0.86 [4 mg/day]; Sallee et al.: 0.43 [2 mg/day] and 0.62 [4 mg/day]).

In addition, there are data demonstrating the efficacy and safety of using either clonidine or guanfacine in combination with stimulants for ADHD. Two randomized, multicenter, double-blind placebo controlled trials looked at immediate-release clonidine given adjunctively with MPH (Palumbo et al., 2008; Sallee et al., 2013; Tourette's Syndrome Study Group, 2002). Both studies had identical designs but differed in their study populations (Sallee et al., 2013). The Tourette's Syndrome Study Group examined 136 children with ADHD and comorbid chronic tic disorders. The combination of immediate-release clonidine and MPH produced the maximum treatment benefit for both ADHD symptom reduction and improvement in tics. In a sixteen-week, randomized, multicenter, double-blind, placebo-controlled study by Palumbo and colleagues (2008), 122 children (aged 7 to 12 years) with ADHD were randomized to receive placebo, immediate-release clonidine monotherapy (maximum dose 0.6 mg/day; mean dose 0.24 ± 0.11 mg/day), immediate-release MPH monotherapy (maximum dose 60 mg/day; mean dose 30.2 ± 18.9 mg/day), or combination therapy (mean clonidine dose 0.23 ± 0.13 mg/day; mean MPH dose 25.4 ± 18.2 mg/day). Although clonidine alone demonstrated a clinical benefit, it was inferior to MPH alone or in combination with MPH as measured by the change from baseline on the Connor's Abbreviated Symptom Questionnaire for Teachers (primary

efficacy measure). In an eight-week, randomized, multicenter, double-blind, placebo-controlled trial, 198 children and adolescents (aged 6 to 17 years) with hyperactive- or combined-subtype ADHD, who had an inadequate response to a stimulant, were randomized to receive either extended-release clonidine or placebo in combination with their baseline stimulant regimen (short- or long-acting MPH or amphetamine treatment). To meet inclusion criteria, subjects had to have been treated with a stable dose of either MPH or amphetamine for four weeks prior to screening and had to have an ADHD-RS-IV total score of at least 26. During the first five weeks, clonidine was titrated by 0.1 mg/week to an optimal dose based on improvement on the ADHD-RS-IV total score (primary efficacy measurement) and tolerability. Beginning in week two, extended-release clonidine plus stimulant resulted in a significantly greater improvement in ADHD-RS-IV total scores compared to placebo plus stimulant. Although the overall effect size for extended-release clonidine plus stimulant (0.34) versus stimulant alone was lower compared to monotherapy trials versus placebo alone, there was still a clinically significant improvement with adjunctive treatment over stimulant alone. This study had several notable limitations. First, patients with significant Axis I psychiatric comorbidities (i.e., CD) were excluded. Second, participants' stimulant medication regimens were determined on the basis of their response to a specific regimen (i.e., MPH or amphetamine). Although clinically applicable, this design made it impossible to determine whether specific combinations of stimulant medications were more effective than others. Finally, dosages of stimulant medications were not optimized during the course of the study, so it is unclear what the effects of extended-release clonidine would have been if a formal optimization phase had been used (Kollins et al., 2011).

In 2012, Wilens and colleagues conducted a 9-week, multicenter, double-blind, placebo-controlled, dose-optimization trial of extended-release guanfacine given adjunctively to stimulants. This study examined 461 children and adolescents (aged 6 to 17 years) with ADHD and suboptimal but partial response to stimulants alone. Subjects continued on their stable morning stimulant (short- or long-acting MPH or amphetamine treatment), and they were subsequently randomized to receive optimized extended-release guanfacine(1 to 4 mg/day) in the morning or in the evening, or placebo. Ultimately, both guanfacine treatment groups showed significantly greater improvement from baseline on ADHD-RS-IV total scores compared to placebo. Notably, these results generalized to both younger and older patients. The effect size for morning guanfacine plus stimulant was 0.377; for evening guanfacine plus stimulant it was 0.447. Although the overall effect sizes were low compared to what has been demonstrated in extended-release guanfacine versus placebo trials, symptom improvement with adjuvant treatment was still demonstrated over stimulant alone. Similar to the limitation in the 2011 study by Kollins and colleagues, stimulant medication doses were not optimized (Wilens et al., 2012).

Immediate-release clonidine is FDA approved for the treatment of hypertension but not for the treatment of ADHD (Catapres, 2010). The typical dose of immediate-release clonidine used to treat hypertension in adults is 0.2 to 0.6 mg/day, divided and given two times a day (Catapres, 2010). This is approximately the same dose range used in ADHD studies (Sallee et al., 2013). Similarly, immediate-release guanfacine is FDA approved for the treatment of hypertension but not for the treatment of ADHD, and the typical dose ranges from 1 to 2 mg given once per day (Tenex, 2008).

Only extended-release clonidine (Kapvay) and extended-release guanfacine (Intuniv) are FDA approved as monotherapy or adjuvant therapy for children and adolescents (aged 6 to 17 years) with ADHD. According to prescribing information, extended-release clonidine dosing should begin at 0.1 mg/day given at bedtime. The dose can be increased by 0.1 mg/day weekly until optimal response is achieved. Doses higher than 0.1 mg/day should be administered twice a day with an equal or higher dose given at bedtime, and the approved dose range is 0.1 to 0.4 mg/day (Kapvay package insert, 2010). According to prescribing information, extended-release guanfacine dosing should begin at 1 mg/day. The dose can be increased in increments of no more than 1 mg/week until optimal response is achieved. Dosing of extended-release guanfacine should be maintained within the range of 1 to 4 mg/day for both monotherapy and adjunctive therapy to a stimulant. Clinically relevant improvements were observed beginning at doses in the range 0.05 to 0.08 mg/kg once daily in both monotherapy and adjunctive therapy. Efficacy increases with increasing weight-adjusted dose (mg/kg), and if well tolerated, doses up to 0.12 mg/kg

per day may provide additional benefit (Intuniv package insert, 2011).

The most commonly reported adverse events in clinical trials with α_2-agonists are fatigue, sedation, and hypersomnia (Newcorn et al., 2003), although there is a high likelihood that the initial somnolence will improve over time (Daviss et al., 2008). In general, the extended-release α_2-agonists are better tolerated than the immediate-release formulations. The rapid absorption of the immediate-release α_2-agonists leads to high-peak plasma concentrations that are associated with the side effects of sedation, dry mouth, and hypotension.

The adverse event profile of all guanfacine and clonidine formulations is similar to that which could be expected of any centrally acting α_2-adrenoagonist antihypertensive agent, including small but consistent decreases in pulse and in both systolic and diastolic blood pressure. Reductions in pulse and blood pressure are dose dependent across all studies, and the greatest effects are noted at higher doses (Biederman et al., 2008a; Sallee et al., 2009b). In a study addressing the concerns about the safety and tolerability of clonidine when used alone or in combination with a stimulant in youths, investigators examined changes in electrocardiograms and in vital signs, including orthostatic changes, in a large sample of children with ADHD. All subjects were participating in a randomized placebo-controlled trial of clonidine, with and without MPH. The most notable group difference in electrocardiographic outcomes was the higher rate of bradycardia (heart rate less than 60 beats per minute) in patients taking clonidine, although the bradycardia experienced by the majority of individuals was asymptomatic and of questionable clinical significance. There were no other significant changes in the electrocardiogram patterns between treatment groups (Daviss et al., 2008). Although there has historically been concern about the cardiovascular safety of combining clonidine with a stimulant, a recent extensive review of the literature has alleviated this concern (Sallee et al., 2013). Similarly, trials of both long- and short-acting guanfacine have failed to demonstrate any serious cardiac side effects when used alone or in combination with a stimulant. In long-term safety studies of extended-release guanfacine, cardiovascular adverse events were rare, although small reductions in mean blood pressure and pulse rate were evident at monthly visits (Biederman et al., 2008b; Sallee et al., 2009a). Caution should be used when prescribing guanfacine or clonidine to patients with a history of syncope or its predisposing factors, and patients should be advised to avoid dehydration. Prior to starting an α_2-agonist for the treatment of ADHD, baseline heart rate and blood pressure need to be taken and subsequently checked periodically during treatment or after a dose increase. In addition, patients must be cognizant of the importance of their not stopping treatment abruptly, as this could precipitate rebound hypertension (Sallee et al., 2013).

Modafinil (Provigil) is a centrally acting agent with sympathomimetic properties that is structurally and pharmacologically different from stimulant medications. It is a wakefulness-promoting agent that is FDA approved for the treatment of narcolepsy, obstructive sleep apnea/hypopnea syndrome, shift work sleep disorder, and fatigue associated with multiple sclerosis. It was found to be equivalent to 600 mg caffeine (approximately six cups of coffee) in maintaining alertness and performance in sleep-deprived normal volunteers (Wesensten et al., 2002). The precise mechanism of action has not been determined. Although data pooled from three double-blind, placebo-controlled studies showed modafinil to be an effective treatment for children and adolescents with ADHD (Biederman & Pliszka, 2008), the FDA found the drug to be unfit for use in this population. It was not approved for the ADHD indication primarily due to the severe cutaneous adverse reactions associated with modafinil, including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms involving adult and pediatric patients. The FDA-approved label for modafinil now discourages its use in children for any purpose (FDA Drug Safety Newsletter, 2007).

Selective serotonin reuptake inhibitors are widely prescribed for the treatment of mood and anxiety disorders, but Castellanos (1996) found no signs of their efficacy in the treatment of ADHD symptoms in children in the seven studies ($N = 68$) he reviewed.

MONITORING TREATMENT

The AACAP Practice Parameters recommend that during a psychopharmacological intervention for ADHD, the patient should be monitored for treatment-emergent side effects. The effectiveness of regular monthly visits and dose adjustments based

on tolerability and lingering ADHD symptoms was shown in the MTA Study. Those assigned medication management by NIMH protocol had significantly lower ADHD symptom scores than those followed by providers in the community. Children in the MTA Study had five times the rate of kept appointments, increased feedback from the teacher to the provider, and higher mean MPH total daily doses than children treated in the community. Monitoring can be done through direct visits, by phone calls with the patient and family, or even by e-mail contact. Teacher input should be sought at least once in the fall and once in the spring for patients attending primary, middle, or high school. Monitoring should also follow a predetermined plan that is worked out with the patient, and if a child, with the parents as well. Generally, the schedule of monitoring visits should be weekly during the initial dose-adjustment phase and then should become monthly for the first few months of maintenance. After that, visits can be regularly scheduled but less frequent. During monitoring visits, the clinician should collect information about the exact dose used and the administration schedule for the stimulants, including times of day. The clinician should ask about skipped doses. Questions about common and less common as well as acute and long-term side effects should also be raised by the clinician. Family and clinician should agree whether the patient is to be continued on the same stimulant dose or started on another dose. A new prescription should be written and a new appointment scheduled. The patient should leave with a prescription, a plan for administration, and a possible schedule for telephone contact. Reports of lost medication or requests for early refills or multiple dose increases should be viewed in light of possible drug misuse or diversion. Clinicians should emphasize that the patient should never give medication to friends and relatives. When available, clinicians should check state registries to be sure that the patient is not getting psychostimulant prescriptions from multiple prescribers or pharmacies.

The practitioner and family should agree on the dosing schedule of stimulant treatment. Stimulant medication may be administered daily or only on schooldays, with weekends and holidays off drug. Those patients with more impairing ADHD symptoms may benefit from taking medication 365 days per year. Patients should have their need for continued treatment with stimulant medication verified once per year through a brief period of medication discontinuation. This should be planned for a part of the school year when academic testing is not in progress. Strategies for maintaining adherence to treatment are a key component of monitoring. These include the option to adjust stimulant doses to reduce treatment-emergent adverse events. When an adverse event occurs, the practitioner would do well to assess the impairment induced. Some adverse events may not interfere with the child's health or cause significant interruption of routine. If the adverse event worsens, then dose reduction is indicated. If the dose reduction helps the adverse event but results in an increase of ADHD symptoms, then the clinician may want to consider switching to another stimulant.

The AACAP Practice Parameters suggest that adjunctive pharmacotherapy can be used to deal with a troublesome adverse event when the stimulant treatment is particularly helpful. Stimulant-induced delay of sleep onset may benefit from the use of antihistamines, clonidine, or a bedtime dose of 3 mg melatonin (Tjon Pian Gi, Broeren, Starreveld, & Versteegh, 2003).

CHOICE OF MEDICATION

An international consensus statement (Kutcher et al., 2004), the AACAP ADHD Practice Parameters (2007), the Texas Medication Algorithm Project (Pliszka et al., 2006a), and the American Academy of Pediatrics (2011) all recommend stimulant medication as the first-line of treatment for ADHD. Direct comparisons of MPH and ATX in a double-blind, randomized, multisite trial (Buitelaar et al., 2007; Michelson, 2004) have shown a decided benefit for MPH and confirm the meta-analysis by Faraone and colleagues (2003), which suggested the MPH effect size (0.91) was greater than that of ATX (0.62). However, ATX might take precedence if the family had an aversion to stimulants or the patient had comorbid anxiety, suffered from chronic motor tics, or was an adolescent or adult with a substance abuse problem. The AACAP guidelines recommend that treatment begin with a long-duration formulation of either an amphetamine or an MPH-based stimulant. The specific drug can be chosen based on its rapidity of onset, duration of action, effectiveness in the specific patient under treatment, and insurance coverage. Short-acting stimulants can be used at first for small children or preschoolers if there is

no long-acting preparation available in a low enough dose. Dual-pulse MPH and amphetamine products have strong effects in the morning and early afternoon but tend to wear off by the late afternoon. These drugs work best for children with academic problems at the beginning and middle of the school day, for those whose appetite is strongly suppressed, and for those who have delay of sleep onset during stimulant treatment. Because transdermal stimulants are reported to have higher-than-average numbers of adverse events, orally administered stimulants should be used first. ATX should be employed only if the family does not want treatment with a controlled substance, or if the patient fails to respond to full-dose-range trials of both a long-duration MPH and a long-duration amphetamine preparation. The AACAP Practice Parameters for ADHD (2007) wisely point out that none of the extant practice guidelines should be interpreted as justification for requiring a patient to be a treatment failure (or experience adverse events) with one agent before allowing the trial of another.

CONCLUSIONS

Psychostimulant medications have become a mainstay in the treatment of ADHD, primarily based on their proven efficacy during short-term controlled studies. In fact, the majority of children with ADHD will respond to either MPH or DEX, so that nonresponders are uncommon (Elia et al., 1991). Although the long-term response of ADHD children to psychostimulants has not been examined in a controlled study much longer than 24 months (Jacobvitz et al., 1990), anecdotal reports suggest that patients relapse when their medication is withdrawn and respond when it is restarted. Optimal treatment involves initial titration to optimize dose, followed by regular appointments and a clinician who remains in frequent contact with the patient, parent, and school (Greenhill et al., 2001b). The combination of behavioral and medication therapies is only slightly more effective in reducing ADHD symptoms than medication alone (MTA Cooperative Group, 1999).

Although psychostimulant treatment research has flourished, there is ample opportunity for more studies. Not all patients respond to psychostimulants, in particular patients with comorbid psychiatric disorders. It is also important to determine medication effects on the acquisition of social skills in ADHD children (Hinshaw, 1991). Finally, there remains a need for more long-term psychopharmacological studies as well as studies that target populations with comorbid disorders (e.g., the child with ADHD and a comorbid anxiety disorder) to examine differential responses to medications in these patients.

PSYCHOPHARMACOLOGICAL TREATMENT FOR DISRUPTIVE BEHAVIOR DISORDERS

The psychopharmacological treatment of ADHD often includes managing patients' aggression or their symptoms of either ODD or CD. The essential features of ODD are a recurrent pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness. ODD often precedes the development of CD. The essential features of CD are a repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated (American Psychiatric Association, *DSM-5*, 2013). Discussions of the treatment of these complex disorders involve not only the efficacy and safety of various medications but also the use of multiple psychopharmacological agents of different classes, the optimal behavioral measures to track clinical progress, and the need to target both overt physical aggression toward people or objects and verbal aggression and covert, nonconfrontational aggression (stealing or vandalism).

Disruptive behavior disorders (DBDs), including both ODD and CD, are the most common comorbidities associated with ADHD. Of children with ADHD referred to psychiatric clinics, up to 50% meet criteria for both ADHD and CD (Newcorn et al., 2001). In the MTA Study, 39.9% of the children with ADHD met criteria for comorbid ODD and 14.3% met criteria for CD (MTA Cooperative, 1999). A study that examined psychiatric comorbidities in both preschool- and school-age youth found that 63% of preschoolers with ADHD also had ODD, which was similar to the rate found in school-age children with ADHD (Wilens et al., 2002). In nonreferred community samples, up to 30% of children with ADHD exhibit this comorbidity, depending on the rater (Wolraich et al., 1998).

Children with ADHD frequently display impulsive aggression, which can be characterized as reactive, unplanned, and uncontrolled. Although children with ADHD exhibit disruptive behaviors at school and at home, impulsive aggression is not typically

pathognomonic of the condition. In the MTA Study, 267 of the original 579 children (46%) with ADHD displayed clinically significant aggression. Even after receiving medication treatment for ADHD, 44% of the aggressive subgroup remained symptomatic with aggression (Jensen et al., 2007b). Symptoms of impulsive aggression may include nonprofitable damaging of one's own property and a loss of control in front of other people. A second subtype of aggression, referred to as predatory aggression, is goal-oriented, planned, and controlled. Individuals exhibiting this subtype of aggression may hide their aggressive acts and may be able to control their own behavior (Vitiello & Stoff, 1997b). Notably, the more affective/impulsive and less predatory subtype of aggression is thought to be more responsive to pharmacological intervention (Malone et al., 1998).

Three major clinical consensus conferences have been held to address the pharmacological management of aggression in children and adolescents. These include the Treatment Recommendations for the use of Antipsychotics for Aggressive Youth (TRAAY; Pappadopulos et al., 2003; Schur et al., 2003), revision of the Texas Children's Medication Algorithm (Pliszka et al., 2006a), and Treatment of Maladaptive Aggression in Youth (TMAY; Scotto Rosato et al., 2012). As a general principle, expert opinion strongly supports the use of evidence-based psychosocial interventions (e.g., behavior therapy and parent management training) and parent education and training prior to using medication for maladaptive aggression. This discussion will focus on the current psychopharmacological treatments of choice for children and adolescents with DBDs (ODD and CD) and aggression, while the psychosocial treatments are discussed in a separate chapter 5.

Several assessment scales are frequently used to assess the efficacy of psychopharmacological treatment for DBDs. The Rating of Aggression Against People and/or Property Scale (RAAPP) (Kemph et al., 1993) is a global assessment of aggression completed by the clinician and scored on a five-point scale with 1 indicating "no aggression" and 5 indicating "intolerable aggression." Another scale is the Conduct Disorder Subscale on the Nisonger Child Behavior Rating Scale (NCBRF; Aman, Tassé, Rojahn, & Hammer 1996). The parent-completed NCBRF has various subscales that measure both positive social interactions and various problem behaviors. Higher scores on the problem behavior subscales indicate behavioral dysfunction. The Modified Overt Aggression Scale (MOAS; Kay et al., 1988) is a sixteen-item scale that asks the clinician to rate a patient's aggression (verbal aggression, aggression against property, auto-aggression, and physical aggression) over the previous week. Finally, the Children's Aggression Scale-Parent (CAS-P) and the Children's Aggression Scale-Teacher (CAS-T) (Halperin et al., 2002, 2003) retrospectively measure the frequency and severity of four types of aggression: verbal aggression, aggression against objects and animals, provoked physical aggression, and initiated aggression.

FDA-Approved Medications for ADHD: Psychostimulants, Alpha-2 Agonists, and Atomoxetine

Not only do psychostimulants significantly improve the core symptoms of ADHD, but they also reduce overt aggression in children and adolescents with non-comorbid ADHD, although the effect is less robust in the presence of comorbid ODD and CD (Connor et al., 2002). Connor's meta-analysis of 28 studies between 1970 to 2001 reported on the effect sizes for stimulants on overt and covert aggression-related behaviors in children with ADHD, separated from stimulant effects on the core symptoms of ADHD. The overall effect size was 0.84 for overt and 0.69 for covert aggression-related behaviors in ADHD. Comorbid CD was associated with diminishing stimulant effect size for overt aggression. For example, in a double-blind placebo-controlled RCT of 84 patients (aged 6 to 15 years) with CD, MPH was superior to placebo in reducing both core symptoms of ADHD and antisocial behaviors specific to CD. Nonetheless, symptoms of CD at endpoint were not generally normalized (Klein et al., 1997). Klein and colleagues hypothesized that stimulants are effective in treating both ADHD and CD because these medications target impulsivity, which may be the key pathologic abnormality in both disorders.

In addition to stimulants, α_2-agonists and ATX, both FDA-approved agents for the treatment of ADHD, have shown promise in reducing aggression in patients with ADHD and comorbid ODD or CD. There are few data from type 1 RCTs demonstrating the efficacy of these agents in treating children and adolescents with DBDs and comorbid ADHD (Table 4.4).

TABLE 4.4 FDA-Approved Medications Used for Disruptive Behavior Disorders

Study (Year)	N	Age Range	Inclusion Criteria	Medication Dosage (mean or range)	Design (Duration)	Primary Outcome Measure(s)	Treatment Response	Comment
Stimulants								
Klein et al. (1997)	84	6–15 years	CD	MPH 41.3 mg/day (divided into morning and noon administration)	Double-blind placebo-controlled RCT (5 weeks)	CPRS QRBC	MPH > Placebo	Comorbid ADHD: 69%; MPH effects on CD independent of severity of initial ADHD symptoms
Spencer et al. (2006)	308	6–17 years	ODD or ODD with comorbid ADHD	MAS XR* 10–40 mg/day	Double-blind placebo-controlled forced-dose escalation RCT. Randomized to MAS X*R 10, 20, 30, or 40 mg/day (4 weeks)	SNAP-IV ODD parent rating subscale	MAS XR* (30 and 40 mg/day) > Placebo	Comorbid ADHD: 79.2% Lack of treatment response when analysis limited to patients without comorbid ADHD (21%)
Sinzig et al. (2007)	85	6–16 years	ADHD with comorbid oppositional and aggressive behavior	MPH-MR† (20–30 kg, max 20 mg; 31–50 kg, max 40 mg; >50 kg, max 60 mg)	Double-blind placebo-controlled (5 weeks)	ODD/CD-symptom checklist	MPH-MR† > placebo in decreasing oppositional symptoms; degree of symptom improvement: school > home	Comorbid ODD/CD: 64.7%
Blader et al. (2010)	65	6–13 years	ADHD with comorbid DBD (CD or ODD) and stimulant-refractory aggression	OROS MPH 18–90 mg/day (mean dose for responders: 52.33 mg/day)	Open stimulant monotherapy optimization protocol	MOAS	Aggression among 49.3% of children was reduced sufficiently after stimulant dosage adjustment	All families received behaviorally oriented psychosocial treatment.
Alpha-2 Agonists								
Connor et al. (2000)	24	6–16 years	ADHD with comorbid DBD (CD or ODD)	Clonidine 0.17 mg/day MPH 32.5 mg/day	Double-blind RCT group comparison of MPH vs. clonidine vs. MPH + clonidine (12 weeks)	DBS	MPH = clonidine = MPH + clonidine in symptom reduction of ODD or CD symptoms on the DBS	

Hazell et al. (2003)	67	6–14 years	ADHD with comorbid DBD (CD or ODD)	Clonidine 0.10–0.20 mg/day	Double-blind placebo-controlled RCT of adjuvant clonidine added to stimulant for hyperactivity and aggression (6 weeks)	CPRS-RS (Conduct and hyperactivity subscales)	• Clonidine > Placebo in reducing conduct symptoms • Clonidine = Placebo in reducing hyperactive symptoms	Treatment effect on conduct scale not apparent until about 5th week
Connor et al. (2010)	217	6–12 years	ADHD with oppositional symptoms (ODD included)	Guanfacine XR 1–4 mg/day	Double-blind placebo-controlled dose-optimization RCT (9 weeks)	CPRS-RL (Oppositional subscale)	Guanfacine XR > Placebo	Medication washout (including stimulants) prior to randomization
Atomoxetine								
Bangs et al. (2008)	226	6–12 years	ADHD with comorbid ODD/CD	ATX 1.2–2.4 mg/kg per day	Double-blind placebo-controlled RCT (8 weeks)	SNAP-IV ODD and ADHD subscales	• ATX = Placebo for ODD at 8 weeks (end of study) but medication was superior to placebo at 2 and 5 weeks. • ATX > placebo for ADHD	Medication washout (including stimulants) prior to randomization
Dell'Agnello et al. (2009)	156	6–15 years	ADHD with comorbid ODD/CD and non-responders to previous 6-week parent support phase	ATX 1.10 ± (SD: 0.13) mg/kg per day	Double-blind placebo-controlled RCT (8 weeks)	SNAP-IV ODD and ADHD subscales	ATX > placebo for both ADHD and ODD	
Dittman et al. (2011)	180	6–17 years	ADHD with comorbid ODD/CD	ATX 1.2 mg/kg per day day administered in fast vs. slow up-titration	Double-blind placebo-controlled RCT (9 weeks)	SNAP-IV ODD and ADHD subscales	• ATX > placebo for both ADHD and ODD • Slow up-titration = fast up-titration in terms of efficacy • Slow up-titration > fast up-titration in term of tolerability	Medication washout (including stimulants) prior to randomization

*MAS XR: mixed amphetamine salts extended release (*Adderall XR*)

†MPH-MR: Medikinet retard® (modified-release MPH preparation with a two-step dynamic to release MPH: 50% immediate release, 50% sustained release; available in Germany and other European countries)

SCALES: CPRS: Children's Psychiatric Rating Scale, CPRS-RL: Conners' Parent Rating Scale–Revised Long Form, CPRS-RS: Conners' Parent Rating Scale–Revised Short Form, DBS: Disruptive Behavior Scale, MAOS: Modified Overt Aggression Scale, QRBC: Quay Revised Behavior Checklist, SNAP-IV: Swanson, Nolan, Pelham-IV.

Second-Generation Antipsychotics

Antipsychotic agents have also been used to control disruptive behavior (with or without comorbid ADHD), particularly when aggression is a core feature. In the 1980s, first-generation antipsychotics such as haloperidol, thioridazine, and molindone were studied in aggressive children with CD and were found to be superior to placebo. However, their side effect profile included sedation and extrapyramidal symptoms, making these agents difficult to tolerate, so the focus has shifted to second-generation antipsychotics (Findling, 2008). The efficacy and safety of these agents (also known as atypical antipsychotics), including risperidone, olanzapine, quetiapine, and aripiprazole, in treating aggressive children with CD and other DBDs has been examined by multiple studies in the past decade, although the majority of these trials are not type I RCTs. The pharmacological mechanism of action through which second-generation antipsychotics may inhibit aggression is not understood, but some investigators have suggested that they exert their antiaggressive action by blocking dopamine and serotonin (Schur et al., 2003).

Risperidone is the most frequently studied atypical antipsychotic and has the largest number of published type I RCTs for treating pediatric aggression in patients with both normal and low intellectual functioning. In addition, risperidone has the FDA indication for the treatment of irritability in children and adolescents (aged six to fifteen) with autism. The majority of patients examined in studies who have a diagnosis of DBD (CD, ODD, or DBD not otherwise specified with aggression) also have comorbid ADHD. There are seven randomized placebo-controlled trials that assessed the acute efficacy and safety of risperidone and one study that assessed time to symptom recurrence over a six-month period of maintenance treatment (Loy et al., 2012). In the earliest of these short-term trials, Findling and colleagues randomized 20 children and adolescents (aged 5 to 15 years) with average intelligence and primary CD to risperidone or placebo. The primary outcome measure used in this study was the RAAPP. Risperidone, in relatively low doses (0.75 to 1.5 mg/day), was superior to placebo in improving aggression on most measures and was reasonably well tolerated. None of the risperidone-treated youth developed extrapyramidal side effects, and the most common side effect was weight gain (Findling et al., 2000). In two additional small and short-term RCTs, youth with DBDs and subaverage intelligence (CD, ODD, and ADHD with persistent and overt aggression) who were randomized in a parallel fashion to either risperidone or to placebo showed significant improvement on the primary outcome measure (Buitelaar et al., 2001; Van Bellingham & Troch, 2001). Notably, in the Buitelaar study, the participants were selected from two inpatient settings, and their aggressive behavior had to have failed to respond to behavioral treatment approaches. In the Van Bellinghen study, patients were selected from residential care settings.

In addition, there are two larger scale 6-week outpatient multicenter double-blind placebo controlled trials in youth (aged 5 to 12 years) with DBDs and subaverage intelligence. Aman and colleagues conducted a parallel-group trial of risperidone in 118 children with severe DBDs, including CD, ODD, or DBD not otherwise specified, and subaverage intelligence (IQs 36 to 84). Fifty-nine percent of the subjects had comorbid ADHD and were permitted to remain on a psychostimulant if the dose had been stable for at least 30 days prior to the start of the study. Patients were randomly assigned to receive risperidone at a weight-adjusted dose of 0.02 to 0.06 mg/kg per day or placebo (mean dose at endpoint 1.16 mg/day) (Aman et al., 2002). By the first week of treatment, there was a significantly greater reduction in symptom severity with risperidone compared to placebo on the primary outcome measure (mean change from baseline on the Conduct Problem Subscale of the NCBRF). A parallel multicenter study by Snyder and colleagues that used the same selection criteria, experimental design, and dosing scheme enrolled a total of 110 patients (Snyder et al., 2002). Comparable to the Aman study, Snyder and colleagues reported a significantly large percentage of subjects with comorbid ADHD, specifically 80% of participants. The mean dose of risperidone was 0.98 mg/day, and there was a similar reduction in symptom severity on the Conduct Problem Subscale of the NCBRF. A subanalysis showed that the effect of risperidone was unaffected by diagnosis, presence/absence of ADHD, stimulant use, IQ, or somnolence (Snyder et al., 2002). Somnolence was the most commonly reported side effect with risperidone in both multicenter RCTs (Aman et al. 51%; Snyder et al. 41.5%). Nonetheless, somnolence was generally mild and transient in both studies and led to discontinuation in only two subjects. Notably, in both studies, the positive effects of risperidone on behavior measures were

shown to be independent of the sedative effects. In addition, there was significant weight gain with risperidone compared to placebo in both studies, with mean weight increases of 2.2 kg and 0.9 kg (Aman et al.) and 2.2 kg and 0.2 kg (Snyder et al.) in the risperidone and placebo groups, respectively. Finally, in both studies, prolactin levels increased with risperidone versus placebo, but there were no clinically significant adverse events related to elevated prolactin levels.

Although there are numerous type 1 RCTs supporting the clinical utility of risperidone for the acute treatment of DBDs (CD, ODD), particularly in youth with subaverage intelligence, there is only one RCT that examines the efficacy of long-term maintenance treatment in a sample of patients with average intelligence (Reyes et al., 2006). During the first 12 weeks of treatment, 527 patients (aged 5 to 17 years) of normal intelligence with DBDs (CD, ODD, or DBD not otherwise specified) received 6 weeks of open-label risperidone that was flexibly dosed based on body weight (acute phase). For patients weighing less than 50 kg, their dose range was 0.25 to 0.75 mg/day, and for patients weighing 50 kg or above, their dose range was 0.5 to 1.5 mg/day. Subsequently, responders entered continuation treatment, defined as 6 weeks of single-blind risperidone at the same dose taken during the acute phase. Of the initial 527 patients, 335 youth exhibited sustained response and were randomly assigned to 6 months of double-blind treatment with either risperidone or placebo. During the 6-month maintenance phase, patients randomized to risperidone were continued on the same dose they had been taking during the continuation phase, which could not be adjusted. The primary efficacy measure was the time to symptom recurrence, defined as deterioration of at least 2 points on the Clinical Global Impression Severity Rating Scale (CGI-I) or 7 points on the Conduct Problem Subscale of the NCBRF. Risperidone was effective for relapse prevention; the rate of relapse was significantly higher in the placebo group (42%) than in the risperidone group (27%). Youth who continued risperidone also had a significantly longer time to symptom recurrence compared to those switched to placebo. The time until 25% of the patients experienced symptom relapse was 119 days in the risperidone group versus 37 days in the placebo group (Reyes et al., 2006). Similar to the populations examined in the short-term RCTs of risperidone in the management of DBDs, there was a large percentage of patients in this study with comorbid ADHD (67%), and 24% of the overall population were taking stimulants.

As part of the 2012 Cochrane Review of atypical antipsychotics for disruptive behavior, data pooled from two trials (Aman et al., 2002; Findling et al., 2000) (combined N = 138) demonstrated that participants on risperidone gained 2.37 kg on average more than those in the placebo group over 6 to 10 weeks of treatment (Loy et al., 2012). Because there are very limited longer-term data, it is unclear whether the effect will weaken or worsen over time. There are also minimal data regarding metabolic side effects in these studies. In regards to potential long-term side effects, there does not seem to be an association between risperidone and adverse changes in height or pubertal development, which need to be considered when administering pharmacotherapy to children and adolescents. Dunbar and colleagues compared the observed versus the expected outcomes for height and sexual maturation in pooled data from five studies that included 700 children and adolescents (aged 5 to 15 years) with disruptive behavior disorders. Patients receiving up to 12 months of risperidone had an average increase in height that was 1.2 cm greater than the reference population. There was also no delay in sexual maturation, measured according to Tanner staging, in risperidone-treated patients.

Although elevated prolactin levels have been found to accompany treatment with risperidone, these elevated levels have not been associated with abnormal growth or delayed sexual maturation in short-term studies (Dunbar et al., 2004). In another examination of the data collected from five trials, Findling and colleagues looked at the possible association between adverse events and the elevated prolactin levels found in patients treated with risperidone over the long term. Although youth treated with risperidone had an initial increase in prolactin levels, predominantly during the first 2 months of treatment, prolactin levels slowly decreased over 1 year of treatment. At least one side effect hypothetically attributable to prolactin (i.e., amenorrhea and hirsutism in girls, erectile dysfunction and galactorrhea in boys, and breast enlargement, decreased libido, osteoporosis, and failure to enter or progress through puberty in both girls and boys) was reported in 2.2% of children, but no direct correlation between hyperprolactinemia and these side effects was found (Findling et al., 2003).

Quetiapine has shown benefit in treating DBDs and aggression. This includes one small RCT of 9 patients (aged 12 to 17) with CD, and one small 8-week open-label single-site study of 17 youth (aged 6 to 12) with CD and the corresponding 18-week open-label extension trial (Connor et al., 2008; Findling et al., 2006, 2007). Connor and colleagues randomized 9 youth with CD (co-morbid ADHD: 79%) to 7 weeks of quetiapine or placebo. Quetiapine was dosed twice daily and could be titrated through the end of week 5. The dose was held constant for the final 2 weeks of the study, and the mean dose of quetiapine was 294 ± 78 mg/day. Quetiapine was found to be superior to placebo on the primary outcome measures, Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I) scales.

Limited data exist for the treatment of DBDs with aripiprazole. Although there are no type 1 RCTs, there are two small open-label studies of aripiprazole for the treatment of CD. Findling and colleagues enrolled 23 youth (ages 6 to 15 years) in an open-label study to evaluate the dosing, safety, and effectiveness of aripiprazole in children and adolescents with CD. At the end of 15 days, approximately 52% of study participants responded to treatment, as evidenced by improvements in RAAPP scores and CGI-S scores based on clinician and parent observations (Findling et al., 2009). Kuperman and colleagues found a reduction in aggressive behavior in ten adolescent boys (aged 13 to 17 years) as measured by the total score on the MOAS and the CAS-P. In both studies, the initial aripiprazole dose depended on the weight of the patient: less than 25 kg, 1 mg/day; 25 to 50 kg, 2 mg/day; 51 to 70 kg, 5 mg/day; and more than 70 kg, 10 mg/day (Kuperman et al., 2011). The maximum dose was 15 mg/day and 20 mg/day in the Findling and Kuperman studies respectively.

There are scant published data on the use of olanzapine in treating DBDs, with no type 1 RCTs. Handen and colleagues conducted an 8-week open-label prospective trial of olanzapine in 16 adolescents (aged 13 to 17 years) with DBDs (CD, OD, DBD not otherwise specified, or ADHD with significant irritability and disruptive behavior). Dosing ranged from 5 to 20 mg/day, with an average dose of 13.7 mg/day. Although there was statistically significant improvement on the Irritability and Hyperactivity subscales of the Aberrant Behavior Checklist (ABC; Aman et al., 1985) and on the Conners' Parent Rating Scale Hyperactivity Index from the parent version of the Conners' Scale (Goyette et al., 1978), four subjects discontinued prematurely due to worsening symptoms or side effects. Weight gain was the most common side effect, with a mean weight gain of 12.7 pounds (Handen & Hardan, 2006). Masi and colleagues examined the efficacy and tolerability of olanzapine (mean dose 8 ± 3.2 mg/day) in a retrospective chart review of 23 youth with CD who had not adequately responded to mood stabilizers or nonpharmacological interventions. Subjects were followed for 6 to 12 months. Based on both an improvement of at least 50% on the MOAS, and a score of 1 or 2 on CGI-I, 60.9% of subjects responded to treatment with olanzapine. Mean weight gain at the end of the follow-up was 10 ± 6.6 pounds (Masi et al., 2006).

To date, there are no published studies examining the effects of ziprasidone on aggression. However, there are unpublished data investigating the efficacy, safety, and tolerability of ziprasidone versus placebo in the treatment of CD, ODD, and DBD not otherwise specified in older children and adolescents in an outpatient study (Shulz, unpublished data; http://clinicaltrials.gov/show/NCT00676429).

Psychostimulants Augmented with Second-Generation Antipsychotics

There is also limited evidence for the efficacy of combining psychostimulants with atypical antipsychotics in treating ADHD comorbid with DBDs. Importantly, no studies have specifically compared monotherapy with second-generation antipsychotics to combination treatment (Linton et al., 2013). In the sole randomized double-blind placebo-controlled study of combination therapy, Armenteros and colleagues added risperidone for treatment-resistant aggression in youth with ADHD who had not sufficiently responded to a psychostimulant alone. In this small pilot study, they randomized twenty-five children (aged 7 to 12 years) with ADHD and significant aggressive behaviors to receive either risperidone (mean dose: 1.08 mg/day) or placebo for 4 weeks. Youth were already in treatment with a constant dose of a stimulant medication for at least 3 weeks before entering the study and remained on this dose. Although ADHD symptoms may have improved, aggressive behaviors had failed to respond to stimulant medication alone. The primary efficacy measures were changes from baseline on the total scores of the CAS-P and the CAS-T (Halperin et al., 2002, 2003). After 4 weeks, risperidone augmentation of psychostimulant

treatment produced a significant reduction in aggressive behaviors (decrease of at least 30% in CAS-P total score) compared to augmentation with placebo. Nonetheless, there were no differences in the individual subscales of the CAS-P or in the CAS-T total score or in any of its subscales. There was also a large placebo response rate (Armenteros et al., 2007). Greater than 10% of the risperidone treatment group experienced abdominal pain and vomiting, but no one discontinued treatment. Notably, there was neither a significant difference in weight gain nor in BMI between treatment groups. This result is certainly unusual compared to the majority of studies with second-generation antipsychotics that have demonstrated a significant amount of weight gain, although the small size and brief duration of this study limit its ability to detect significant differences (Armenteros et al., 2007).

In another antipsychotic/stimulant combination study, Kronenberger and colleagues examined the efficacy and safety of adding quetiapine to OROS-MPH for comorbid ADHD and DBD. This was a prospective open-label study of adjuvant quetiapine for youth (aged 12 to 16) with ADHD and comorbid DBDs (CD or ODD) and moderate aggressivity who had not adequately responded to MPH monotherapy. Twenty-four youth received 3 weeks of OROS MPH monotherapy titrated up to 54 mg/day. Those subjects, who remained symptomatic, subsequently received 9 weeks of adjuvant quetiapine (mean dose: 392.2 mg/day). At the conclusion of the study, the addition of quetiapine to OROS-MPH effectively reduced ADHD and aggression (as per the CGI-I, RAAPP, and ADHD-RS-IV criteria for significant improvement) in individuals who did not respond sufficiently to OROS-MPH alone. Mild and transient sedation was reported by about half of treatment subjects. Initial weight loss (1.98 pounds) during MPH treatment was offset by weight gain (2.65 pounds) during combination treatment (Kronenberger et al., 2007). Similarly, two post hoc reviews of data from naturalistic cohort studies found that stimulant therapy did not provide a significant protective effect against the weight gain and metabolic changes associated with second-generation antipsychotics (Carlage et al., 2009; Penza et al., 2009).

Mood Stabilizers

Mood stabilizers, such as lithium and divalproex, have also been shown to be effective in treating aggression in youth with DBDs. In two small type 1 RCTs, lithium was superior to placebo in measures of global improvement and in reduction of aggression in children and adolescents with CD in an inpatient setting (Campbell et al., 1995; Malone et al., 2000). In the only negative RCT that reported that lithium was not more effective than placebo in reducing CD symptoms, lithium was administered for only 2 weeks versus 6 weeks in the studies showing efficacy (Rifkin et al., 1997). Clearly, one of the major downsides to treatment with lithium is the need to closely monitor blood levels to prevent toxicity.

Divalproex was found to be superior to placebo in a small crossover RCT of youth with DBDs, explosive temper, and mood lability (Donovan et al., 2000). Steiner and colleagues randomized 71 adolescents with CD who were living in a residential facility for juvenile offenders to either therapeutic or low doses of divalproex for 7 weeks. Both subjects and clinicians were blinded to treatment status. Symptom severity and global improvement ratings were more favorable after administration of higher/therapeutic doses (500 to 1,500 mg/day) than lower doses (up to 250 mg/day) of divalproex (Steiner et al., 2003).

Divalproex has also been examined as an augmenting agent with psychostimulants for reducing aggression among children with ADHD and a DBD, whose chronic aggression was refractory to optimized stimulant treatment alone. Youth (aged 6 to 13 years) diagnosed with ADHD and either ODD or CD were recruited into a treatment study with an open 5-week lead-in phase of stimulant monotherapy and family-focused behavioral management treatment (Blader et al., 2009), where the goal was to identify the optimal agent and dose for each child. Subsequently, subjects whose aggressive behavior persisted at the end of 5 weeks were randomized in a double-blind fashion to receive divalproex or placebo as an adjuvant treatment for 8 weeks. Adjuvant divalproex (mean dose: 567 mg/day; mean serum valproic acid level: 68 mg/liter) was more effective than adjuvant placebo in decreasing aggressive behavior: 57% of subjects randomized to divalproex met remission criteria compared to 15% of those assigned to placebo. Finally, carbamazepine was not superior to placebo for reducing aggressive behavior in the one double-blind placebo-controlled trial of subjects with aggressive CD (Cueva et al., 1996).

Before initiating psychopharmacological treatment to target impulsive aggression in children and

adolescents with DBDs, the clinician should consider using psychosocial interventions. This is particularly important since the second-generation antipsychotics like risperidone, which has the most data supporting its efficacy, can cause weight gain and or metabolic side effects.

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5

Psychosocial Treatments for Conduct Disorder in Children and Adolescents

Alan E. Kazdin

Antisocial and aggressive behavior (conduct disorder [CD]) is a severe source of impairment among children and adolescents in light of the stability of the problem, the untoward long-term prognosis, and the diverse domains of dysfunction in the child, parent, and family with which the problem is associated. Significant advances have been made in treatment. Several psychosocial interventions with strong evidence in their behalf with children and adolescents are highlighted and include parent management training, multisystemic therapy, multidimensional treatment foster care, cognitively based treatments, functional family therapy, brief strategic family therapy, and the Good Behavior Game. The treatments have been very well studied with multiple replications. There are some commonalities among the treatments. Two that are salient are the use of techniques of applied behavior analysis (e.g., operant conditioning as a means of behavior change) and focus on the family. These are not part of all of the techniques covered but encompass most of them. Also, the set of treatments as a whole has addressed the full range of severity of dysfunction and age through childhood and adolescence. Thus, the evidence applies to oppositional and conduct problems in early childhood, severe aggressive and antisocial behavior at home and at school among children referred for either inpatient or outpatient treatment, and adolescents who have been adjudicated for serious acts of delinquency. Outcomes have been reflected on a range of measures and indices of antisocial behavior, including psychological measures of impairment and symptoms but also on dropping out of school, substance use, pregnancy rate, criminal activity, hospitalization, and readjudication. There remain questions about the long-term impact of treatments, the persons for whom one or more of these treatments is well suited, and how to optimize therapeutic change. Disseminating effective interventions to professionals in clinical practice and reaching the majority of children in need who do not receive treatment remain critical challenges. Even so, the extensive evidence indicates that there are several viable treatments for CD.

INTRODUCTION

Antisocial behavior in children refers to social rule violations and actions against others and includes such behaviors as fighting, lying, and stealing. Many such behaviors are evident in varying degrees over the course of child development. CD refers to antisocial behavior that clearly is beyond the realm of "normative" functioning in light of its frequency, persistence, intensity, and impact on others (e.g., parents, teachers, peers), and whether it leads to significant impairment of the child. CD is currently recognized as a psychiatric disorder with a constellation of symptoms, likely history, and long-term course.

The significance of CD as a clinical and social problem derives from several factors (e.g., Colman et al., 2009; Hill & Maughan, 2001; Loeber, Burke, & Pardini, 2009; Murray & Farrington, 2010). The

behaviors that constitute CD are among the most frequent bases of clinical referral in child and adolescent treatment services and encompass from one third to one half of referred cases. Moreover, children with CD often traverse multiple social services in childhood, adolescence, and adulthood (e.g., special education, mental health, juvenile justice). This contributes to the fact that CD is one of the most costly mental disorders in the United States. The estimated cost for a child with CD is $10,000 to $15,000 per year for social services over the course of childhood and adolescence (Bonin et al., 2011; Foster & Jones, 2005; Scott, Knapp, Henderson, & Maughan, 2001). These costs are 10 times greater than for a child without the diagnosis.

Fortunately, significant advances have been made in developing effective interventions, in relation to both treatment and prevention (see Baldwin et al., 2012; Christopherson & Vanscoyoc, 2013; Steele, Elkin, & Roberts, 2008; Weisz & Kazdin, 2010). This chapter reviews advances in psychosocial treatments for CD and aggressive and antisocial behavior more generally. The treatments were selected because they have been carefully evaluated in randomized controlled clinical trials with children and adolescents.[1] The chapter describes and evaluates the current techniques and highlights evidence in their behalf. Issues that influence interpretation of the evidence and current and future research directions are discussed.

CHARACTERISTICS OF CONDUCT DISORDER: OVERVIEW

Descriptive Features: Diagnosis and Prevalence

CD reflects a persistent pattern of behavior in which the rights of others and age-appropriate social norms are violated. Isolated acts of physical aggression, property destruction, stealing, fire setting, and running away are sufficiently severe to warrant concern and attention in their own right. Although these behaviors may occur in isolation, several are likely to appear together as a constellation or syndrome and form the basis of a clinical diagnosis. For example, in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*; American Psychiatric Association [APA], 2013), the diagnosis of CD is merited if the child shows at least three of 15 symptoms within the past 12 months, with at least one symptom evident within the past 6 months. The symptoms include bullying others, initiating fights, using a weapon, being physically cruel to people or to animals, stealing items of nontrivial value, stealing while confronting a victim, forcing someone into sexual activity, fire setting, destroying property, breaking into others' property, staying out late, running away, lying, and truancy.

Using these diagnostic criteria or criteria from prior versions of the *DSM*, the prevalence of the disorder among community samples of school-age youth is approximately 2% to 10% (median 4%; APA, 2013). The lifetime prevalence rate is approximately 10% (Nock, Kazdin, Hiripi, & Kessler, 2006). One of the most frequent findings is that boys show approximately three to four times higher rates of CD than girls. The prevalence rates of CD are likely to underestimate the extent of the problem. The criteria for delineating individual symptoms and the diagnosis are recognized to be somewhat arbitrary. Youths who approximate but fail to meet the diagnosis, sometimes referred to as subsyndromal or subclinical, often are significantly impaired. CD is better represented as a spectrum disorder or set of continua based on the number, severity, and duration of symptoms and degree of impairment rather than as a condition achieved by a particular cutoff.

Subtypes and Patterns to Delineate Subgroups

Clearly, CD is not a homogeneous disorder. Indeed, given the diagnostic criteria mentioned previously, over 32,000 distinct symptom profiles can be identified that would qualify for the diagnosis. It is unlikely that CD results from a single cause or set of causes in principle because there is no single or circumscribed pattern that the diagnosis identifies. Research identifying different ways of delineating subgroups of CD makes up a large literature in an effort to refine how to view the disorder(s).

In *DSM-5*, subtypes are recognized based on the age of onset and life course. Box 5.1 summarizes the subtypes. The pattern that reflects a more severe form of the disorder is early onset, which includes aggressive behavior and a worse long-term prognosis than the more common adolescent onset. Longitudinal research has supported key facets of these patterns (Moffitt et al., 2001; Moffitt & Caspi, 2005; Reid, Patterson, & Snyder, 2002). Among the interesting patterns, the higher prevalence rate for of CD boys

BOX 5.1 Currently Delineated Subtypes of Conduct Disorder

Child Onset (a.k.a. Life-Course Persistent)
- Begins in childhood
- Associated with aggressive behavior
- More common among boys
- More likely to show deficiencies in planning, problem solving, and abstract reasoning
- Poor prognosis—more likely to continue into adulthood
- More dropping out of school, more violent crime
- Harsh parenting practices play an important role
- The more severe form of the disorder

Adolescent Onset (a.k.a. Adolescent Limited)
- Begins in adolescence
- More common than child onset
- Associated with vandalism and criminal behavior
- More equally distributed among girls and boys
- Less likely to continue antisocial behavior long term
- Peer group influences play a major role
- The less severe form of the disorder

Discontinuous Offending (a.k.a. Low Level, Chronic)
- Pervasive symptoms, looks like child-onset group
- Rate of the problems not as severe—more sporadic
- Socially isolated and tend to be withdrawn

DSM-5 recognizes the first two and has as a third type, "unspecified onset," when the information is not available. I have included "Discontinuous Offending" as a third type that has emerged in research but is not as well established or as frequent as the first two subtypes (see Moffitt et al., 2008, for a thorough discussion of CD and *DSM* subtypes and related matters).

is associated primarily with childhood-onset CD; the boy-to-girl ratio evens out for adolescent-onset CD. Although onset and life course have evidence in their behalf, the subtypes have not emerged in many analyses of CD, and there are common features that span these subtypes (e.g., Kendler, Aggen, & Patrick, 2013; Nock et al., 2006; Waldman et al., 2011). Also, within a given subtype (e.g., child onset), it is likely that vast distinctions need to be made.

Apart from subtypes, callousness-unemotional interpersonal personality style influences CD. A callous-unemotional style consists of lack of guilt and lack of empathy or remorse (Frick, Ray, Thornton, & Kahn, 2014; Rowe et al., 2010). CD children high in callous-unemotional style are considered to have more severe and persistent symptoms. Also, they are characterized by sensation seeking, less sensitivity to emotional stimuli, and lower levels of anxiety. Callousness has been an extremely active area of research. Overall, subtypes and interpersonal style are useful to convey that advances are being made in delineating facets that might help with the enormous heterogeneity of youth and symptom constellations that constitute CD. As yet, the subtypes and patterns that have been studied do not provide clear guidelines to suggest what treatments to provide or not to provide.

Scope of Dysfunction

If one were to consider "only" the symptoms of CD and the persistence of impairment, the challenge of identifying effective treatments would be great enough. However, the presenting characteristics of children and their families usually raise other considerations that are central to treatment. Consider the characteristics of children, families, and contexts that are associated with CD as a backdrop for later comments on treatment.

Child Characteristics. Children who meet criteria for CD are likely to meet criteria for other disorders as well. The coexistence of two or more disorders is referred to as comorbidity. Although comorbid disorders among youth with CD span the full range of psychiatric diagnoses (Nock et al., 2006), those involving other disruptive or externalizing behaviors (oppositional defiant disorder, attention-deficit/hyperactively

disorder) are especially likely. In my own work (and only one clinic), children referred for CD meet criteria for a mean of 2.4 disorders and occasionally extending up to five disorders (Kazdin, 2010). This conveys that the challenge of treatment is beyond pairing a given treatment with a given disorder.

Children with CD are likely to show academic deficiencies, as reflected in achievement level, grades, being left behind in school, early termination from school, and deficiencies in specific skill areas such as reading. Youths with the disorder are likely to evince poor interpersonal relations, as reflected in diminished social skills in relation to peers and adults, bullying, and higher levels of peer rejection. They are likely to show deficits and distortions in cognitive problem-solving skills, attributions of hostile intent to others, and resentment and suspiciousness. Clearly, CD is pervasive in the scope of child characteristics that are affected.

Parent and Family Characteristics. Several parent and family characteristics are associated with CD. Criminal behavior and alcoholism are two of the stronger and more consistently demonstrated parental characteristics. Harsh, lax, erratic, and inconsistent parent disciplinary practices and attitudes often characterize the families of CD children. Dysfunctional relations also are evident, as reflected in less acceptance of their children; less warmth, affection, and emotional support; and less attachment, compared to parents of nonreferred youths. Less supportive and more defensive communications among family members and less participation in activities as a family are also evident. In addition, unhappy marital relations, interpersonal conflict, and aggression characterize the parental relations of antisocial children. Poor parental supervision and monitoring of the child and knowledge of the child's whereabouts also are associated with CD.

Contextual Conditions. CD is associated with a variety of untoward living conditions such as large family size, overcrowding, poor housing, and disadvantaged school settings. Many of the untoward conditions in which families live place stress on the parents or diminish their threshold for coping with everyday stressors. The net effect can be evident in strained parent–child interactions in which the parent's behavior inadvertently sustains or exacerbates the child's antisocial and aggressive behavior (see Capaldi, DeGarmo, Patterson, & Forgatch, 2002). It is likely there are bidirectional effects in which parent stressors influence child behavior but also child behavior contributes to parental stress (Deater-Deckard, 2004).

Quite often the child's dysfunction is embedded in a larger context that cannot be neglected in conceptual views about the development, maintenance, and course of CD or in the actual delivery of treatment. For example, at our outpatient clinical service (Yale Parenting Center), it is likely that a family referred for treatment will experience a subset of these characteristics: financial hardship (unemployment. significant debt, bankruptcy), untoward living conditions (dangerous neighborhood. small living quarters), transportation obstacles (no car or car in frequent repair, state-provided taxi service), psychiatric impairment of one of the parents, stress related to significant others (former spouses, boyfriends, or girlfriends), and adversarial contact with an outside agency (schools, youth services, courts, debt collection). Many of these characteristics can be captured by standardized psychological measures that quantify stress or impairment. However, many characteristics that influence child and family functioning and indeed treatment are more qualitative, idiosyncratic, and not easily assessed (e.g., husbands who stalk their wives and monitor their calls and whereabouts; parents who buy weapons for their children with CD; parents who train their children to shoplift with them; and mothers who use their homes to sell alcohol and sex in the neighborhood). Such events are not always present. However, these are all real examples and, lamentably, not at all rare stories.

Prognosis of Conduct Disorder

Longitudinal studies have consistently shown that CD identified in childhood predicts a continued course of social dysfunction, problematic behavior, and poor school adjustment. The classic studies showed that antisocial child behavior predicts multiple problems in adulthood 30 years later (Robins. 1966, 1978). Youths who are referred for their antisocial behavior, compared to youths with other clinical problems or matched controls without clinical dysfunction, are likely to show psychiatric symptoms, criminal behavior, physical health, and social adjustment in adulthood. Even though CD portends a number of other significant problems, not all children with antisocial behavior will suffer impairment as adults: Among the

most severely antisocial children, fewer than 50% become antisocial adults. If diverse diagnoses are considered, rather than serious antisocial behavior alone, the picture of impairment in adulthood is much worse. Among youths referred for antisocial behavior, over 80% received a diagnosis of some psychiatric disorder as adults.

Additional longitudinal studies have replicated and extended these early findings (e.g., Fergusson et al., 2005; Moffitt et al., 2001; Murray & Farrington, 2010; Olino, Seeley, & Lewinsohn, 2010). The scope of physical as well as psychiatric consequences also has been elaborated. For example, many children with CD have been subjected to abusive parenting practices that predict higher morbidity and mortality rates from serious disease (e.g., heart attack, cancer, respiratory illness) in adulthood (Krug, Dahlberg, & Mercy, Zwi, & Lozano, 2002). In short, the scope of consequences, suffering, and impairment over the life course is quite astounding. Beyond what CD youths suffer as they move to adolescence and adulthood, the suffering of the victims of their acts (e.g., criminal activity, domestic violence) is enormous as well.

Risk Factors for Conduct Disorder

Decades of research have focused on characteristics, events, and experiences that place individuals at risk for CD. Risk factors are antecedents that correlate with a subsequent outcome. Numerous factors have been identified that predispose children and adolescents to CD. Box 5.2 highlights several risk factors. Risk factors convey important information in identifying cases and in generating hypotheses about processes involved in onset and course, and possible causal connections. Yet there are many cautions and complexities that are essential in evaluating these factors.

As for the cautions, unless otherwise demonstrated the risk factors are only correlates. It is easy to assume unwittingly that because risk factors come before the onset of the problem they play a causal role. Many interventions, both treatment and prevention, have focused on correlates as if they were pivotal to the disorder. The complexities convey why the focus is risky. First, a given factor and antisocial behavior may have bidirectional relations, so it is not clear which came first. For examples, parent stress, irritability, and punishment can both precede and follow child antisocial behavior.

Second, it has been tempting to consider risk factors to be part of either the child's genes or environment. However, the interplay here too is complex. Seemingly environmental influences (e.g., parenting practices in the home) have strong genetic components (Dodge, 2009). Similarly, genetic influences on the child may readily influence parental behaviors in ways that promote the occurrence of environmental factors that increase risk (Moffitt & Caspi, 2005). For example, genetically mediated antisocial behavior appears to influence the parenting practices of adoptive parents. Child deviance can promote adverse parenting practices. These comments do not signify that parenting practices are genetically controlled or fixed; they are in a dynamic relation with multiple influences.

Third, some risk factors are proxies for other variables—that is, they reflect and are accounted for primarily by some other variable. For example, teen marriage places the offspring at risk for CD. It is not likely that marrying early per se is the critical influence because teen marriage is associated with antisocial behaviors and delinquency in girls, liaisons with antisocial men, less schooling, and higher domestic violence, each or all of which might be the critical factor, or explain in whole or in part the predictive value of teen marriage.

Finally, an exciting advance in understanding risk factors is evaluation of gene–environment interactions. This area moved forward considerably by the pioneering finding that the effects of maltreatment of children are moderated by a genetic polymorphism (Caspi et al., 2002), Individuals with a history of abuse and a particular allele (related to serotonin) are at much greater risk for antisocial behavior. Among boys with the allele and maltreatment, 85% developed some form of antisocial behavior (diagnosis of CD, personality assessment of aggression, symptoms of adult personality disorder, or court conviction of violent crime) by the age of 26. Replication of these effects and similar findings has underscored the critical role of gene–environment interactions in antisocial outcomes (Foley et al., 2004; Jaffee et al., 2005). Additional work focused on genetic polymorphism related to dopamine has shown that a genetic influence is moderated by environmental experiences (e.g., Lahey et al., 2011). Larger-scale genome-wide associations are increasing and are generating promising leads

BOX 5.2 Factors that Place Youths at Risk for the Onset of Conduct Disorder

Child Factors

Difficult Child Temperament. A more difficult child temperament (on a dimension of "easy to difficult"), as characterized by more negative mood, lower levels of approach toward new stimuli, and less adaptability to change.

Neuropsychological Deficits and Difficulties. Deficits in diverse functions related to language (e.g., verbal learning, verbal fluency, verbal IQ), memory, motor coordination, integration of auditory and visual cues, and "executive" functions of the brain (e.g., abstract reasoning, concept formation, planning, control of attention).

Subclinical Levels of Conduct Disorder. Early signs (e.g., in elementary school) of mild ("subclinical") levels of unmanageability and aggression, especially with early age of onset, multiple types of antisocial behaviors, and multiple situations in which they are evident (e.g., at home, school, the community).

Hyperactive, Impulsive, Oppositional Defiant Disorder. One of these disorders increases risk of academic deficiencies and lower levels of intellectual functioning.

Poor Bonding and Attachment to Conventional Values. Little connection to family life and schoolwork or to others who are bonded to these values.

Parent and Family Factors

Prenatal and Perinatal Complications. Pregnancy- and birth-related complications, including maternal infection, prematurity and low birth weight, impaired respiration at birth, and minor birth injury.

Psychopathology and Criminal Behavior in the Family. Past or current criminal behavior, antisocial personality disorder, and alcoholism of the parent.

Untoward and Coercive Parent–Child Interaction. Harsh (e.g., severe corporal) punishment, inconsistent punishment, and coercive interchanges increase risk.

Poor Monitoring of the Child. Poor supervision, lack of monitoring of whereabouts, and few rules about where youth can go and when they can return.

Poor Quality of the Family Relationships. Less parental acceptance of their children, less warmth, affection, and emotional support, and less attachment.

Early Marriage. Teen marriage of the child's mother.

Marital Discord. Unhappy marital relationships, interpersonal conflict, and aggression of the parents.

Large Family Size. More children in the family.

Sibling with Antisocial Behavior. Presence of a sibling, especially an older brother, with antisocial behavior.

Few Family Activities. Little involvement of the family in activities (e.g., recreation, religious) together

Socioeconomic Disadvantage. Poverty, overcrowding, unemployment, receipt of social assistance (welfare), and poor housing.

School-Related Factors

Characteristics of the Setting. Attending schools where there is little emphasis on academic work, little teacher time spent on lessons, infrequent teacher use of praise and appreciation for schoolwork, little emphasis on individual responsibility of the students, poor working conditions for pupils (e.g., furniture in poor repair), unavailability of the teacher to deal with children's problems, and low teacher expectancies.

The list of risk factors highlights major influences. The number of factors, their influence, and their interactions are more complex than the summary statements noted here. For a more detailed discussion, other sources can be consulted (e.g., Boden, Fergusson, & Horwood, 2010; Hill & Maughan, 2001; Murray & Farrington, 2010).

on the underpinnings of CD (Dick et al., 2010). More generally, the work on gene–environment interactions provides leads in searching for mediators of action but also might provide a stronger basis for subtyping CD.

In general, no single characteristic or risk factor seems to be necessary or sufficient to account for the onset of the disorder. Even though some risk factors are more important than others, the accumulation of factors (i.e., number present) itself is important. One or two risk factors may not increase risk very much. With several risk factors, however, the likelihood of the outcome may increase sharply. Even with the presence of multiple risk factors, however, the outcome is not determined: Some individuals at high risk may not show any dysfunction. Many factors that contribute to reducing risk, referred to as protective factors, have been identified, but these are less well studied than risk factors.

General Comments

CD is conceived as a dysfunction of children and adolescents. The accumulated evidence regarding

the symptom constellation, associated features, and risk factors, as well as the course over the lifespan, attests to the heuristic value of focusing on characteristics of the child. At the same time, there is a child/parent/family/context gestalt that includes multiple and reciprocal influences that affect each participant (child and parent) and the systems in which the participants operate (family, school).

From the standpoint of treatment, the striking feature is the scope of child, parent, and family domains that seem in need of urgent attention. Understandably, treatment proponents often note that treatment must be multifaceted to address the multiple domains in which dysfunction are evident (e.g., Crenshaw & Mordock, 2005; Henggeler et al., 2009). This seemingly obvious conclusion is in great need of empirical attention, a point to which we will return. Even so, clearly the treatment of CD raises enormous challenges well beyond the presenting symptoms that lead to the diagnosis

EVIDENCE-BASED TREATMENTS

Overview

Many different treatments have been applied to youths with CD, including variations of psychotherapy; pharmacotherapy; psychosurgery; home-, school-, and community-based programs; residential and hospital treatment; and social services. Several treatments now have solid evidence on their behalf (primarily from randomized controlled trials [type 1], but also from single-case designs in which groups of individuals and their changes have been rigorously evaluated (Muffihy, Kidman, & Ollendick; 2010; Weisz & Kazdin, 2010).[2] I highlight major treatments below and refer to other sources (e.g., books and review articles) where each has been treated in greater detail.

Parent Management Training

Background and Characteristics of Treatment. Parent management training (PMT) refers to procedures in which parents are trained to alter their child's behavior in the home (Kazdin, 2009). The parents meet with a therapist or trainer, who teaches them to use specific procedures to alter interactions with their child, to promote prosocial behavior, and to decrease deviant behavior. Training derives from two views. The first is the position that conduct problem behavior is inadvertently developed and sustained in the home by maladaptive parent–child interactions. These interactions include directly reinforcing deviant behavior, frequently and ineffectively using commands and harsh punishment, failing to attend to appropriate behavior, and coercive exchanges that exacerbate child disruptive behavior (e.g., Patterson et al., 1992; Reid et al., 2002). The second view focuses on how to develop prosocial behaviors. This view underscores the advances in applied behavior analysis that can be used to alter behavior. Not all parents engage in interactions that promote child antisocial behavior, although they may once these behaviors become evident and all reasonable interaction patterns of influencing the child have been exhausted. The views are not incompatible, yet the latter view is the broader one and explains the utility of parent training across many domains (e.g., autism spectrum disorder, child anxiety, academic skills) and populations (e.g., children, adolescents, the elderly) (e.g., Kazdin, 2013a).

PMT alters the pattern of interchanges between parent and child so that prosocial, rather than coercive, behavior is directly reinforced and supported within the family. This requires developing several different parenting behaviors that include the skilled use of antecedents, behaviors, and consequences; establishing the rules for the child to follow; providing positive reinforcement for appropriate behavior; delivering mild forms of punishment to suppress behavior; negotiating compromises; and other procedures. These parenting behaviors are systematically and progressively developed within the sessions in which the therapist shapes (develops through successive approximations) parenting skills. The behavior-change programs that parents eventually implement in the home also serve as the basis for the focus of the sessions in which the procedures are modified and refined.

Many variations of PMT exist and have emanated from several programs of research and with varying names for the intervention, including Parent Management Training—Oregon Model (Forgatch, Patterson, & Gewirtz, 2013), The Incredible Years (Webster-Stratton & Reid, 2010), Triple P (Sanders, 2012), Parent-Child Interaction Therapy (Zisser & Eyberg, 2010), and PMT of others (Forehand & Long, 2010) and our group (Kazdin, 2009, 2010). While distinctions can be made among different programs,

some of which include additional treatment components, several common characteristics of PMT can be identified.

First, treatment is conducted primarily with the parent(s), who implement several procedures in the home. The parents meet with a therapist, who teaches them to use specific procedures to alter interactions with their child, to promote prosocial behavior, and to decrease deviant behavior. There may be little direct intervention of the therapist with the child. With young children, the child may be brought into the session to help train both parent and child how to interact and especially to show the parent precisely how to deliver antecedents (prompts) and consequences (reinforcement, time out from reinforcement). Older youths may participate to negotiate and to develop behavior-change programs in the home. Second, parents are trained to identify, define, and observe problem behaviors in new ways. Careful specification of the problem is essential for delivering reinforcing or punishing consequences and for evaluating whether the program is achieving the desired goals. Third, the treatment sessions cover social learning principles and the procedures that follow from them, including positive reinforcement (e.g., the use of social praise and tokens or points for prosocial behavior), mild punishment (e.g., use of time out from reinforcement, loss of privileges), negotiation, and contingency contracting. Fourth, the sessions provide opportunities for parents to see how the techniques are implemented, to practice using the techniques, and to review the behavior-change programs in the home. The immediate goal of the program is to develop specific skills in the parents. As the parents become more proficient, the program can address the child's most severely problematic behaviors and encompass multiple problem domains (e.g., school behavior). Over the course of treatment, more complex repertoires are developed, both in the parents and in the child. Finally, child functioning at school is usually incorporated into the program. Parent-managed reinforcement programs for child deportment and performance at school, completion of homework, and activities on the playground often are integrated into the behavior-change programs. If available, teachers can play an important role in monitoring or providing consequences for behaviors at school.

Evidence and Evaluation. Over the past 40 years, many randomized controlled studies of PMT have been completed with youths varying in age and degree of severity of dysfunction (e.g., oppositional, CD, delinquent youth). It is important to underscore that the evidence extends well beyond a handful of isolated type 1 studies. The Oregon Model, the earliest program of research, alone has generated scores of studies that have evaluated PMT, assessed factors that contribute to change, and replicated treatment effects across multiple samples and settings (Forgatch & Patterson, 2010). Other programs of research and scores of isolated studies have built on this foundation (see Lundahl, Risser, & Lovejoy, 2006; Weisz & Kazdin, 2010).

Treatment effects have been evident in marked improvements in child behavior on a wide range of measures, including parent and teacher reports of deviant behavior, direct observation of behavior at home and at school, and institutional (e.g., school, police) records. The effects of treatment have also been shown to bring problematic behaviors of treated children within normative levels of their peers who are functioning adequately in the community. Follow-up assessment has shown that the gains are often maintained for 1 to 3 years, but some reports have extended to 9 to 14 years (e.g., Forgatch, Patterson, DeGarmo, & Beldavs, 2009; Long, Forehand, Wierson, & Morgan, 1994).

The impact of PMT can be relatively broad. The effects of treatment are evident for child behaviors that have not been focused on directly as part of training. Also, siblings of children referred for treatment improve, even though they are not directly focused on in treatment. This is an important effect because siblings of children with CD are at risk for severe antisocial behavior. In addition, maternal psychopathology, particularly depression, decreases systematically following PMT (see Forgatch & Patterson, 2010; Kazdin, 2010). These changes suggest that PMT alters multiple aspects of dysfunctional families.

Several characteristics of the treatment contribute to outcome. Longer duration of treatment improves outcome. Programs vary in duration from weeks to months and have been applied to populations varying in age and severity of dysfunction. Second, specific training components, such as providing parents with in-depth knowledge of social learning principles and using time out from reinforcement in the home, enhance treatment effects. Third, families characterized by many risk factors associated with childhood dysfunction (e.g., socioeconomic disadvantage, marital discord, parent psychopathology, poor social

support) tend to show fewer gains in treatment than families without these characteristics and to maintain the gains less well, but this is not always the case. Socioeconomic disadvantage and maternal mental health problems are the more well-studied factors that attenuate responsiveness of the child to PMT. Attenuated or reduced effects does not mean that PMT has been ineffective but that treatment modifiers have been identified that influence outcome. This point also applies to other treatments highlighted later.

The extensive outcome evidence for the treatment of CD is bolstered by related lines of work. First, many of the core procedures (e.g., use of antecedents, reinforcement, shaping, and fading) have been developed in nonhuman animal research on operant conditioning. That research has allowed evaluation of specific behavior-change procedures (e.g., reinforcement schedules, time out) that translate to applied settings (Kazdin, 2013a). Second, early studies on family interaction established maladaptive interactions as a critical feature in the homes of many children and then demonstrated that changes in these patterns led to reduced aggressiveness in the home (Forgatch & Patterson, 2010). This was a strong move from mere correlates and risk factors of child dysfunction to causal relations supporting the procedures.

Third, and perhaps unique among evidence-based interventions, is application and evaluation of PMT well beyond the confines of conduct problems. The techniques that make up PMT (e.g., various forms of reinforcement and punishment practices) have been effectively applied with parents of children with autism spectrum disorder, language delays, intellectual disabilities, and medical disorders for which compliance with special treatment regimens is required, and with foster parents, military families with deployed parents, homeless parents, and parents who physically abuse or neglect their children (Cooper, Heron, & Heward, 2007; Gewirtz, Erbes, et al., 2011; Kazdin, 2013a). In addition to treatment, PMT has been used as a preventive strategy for children at risk for academic dysfunction and untoward mental health outcomes (e.g., Prinz et al., 2009; Sanders, 2008; Webster-Stratton & Reid, 2010). Finally, multiple variations of PMT from the programs listed previously have been extended internationally, with replicated trials attesting to their efficacy. Thus, independent replications well beyond the original sites have many exemplars.

In light of the diverse and extensive applications, a great deal is known about the procedures and parameters that influence the reinforcement and punishment practices that form the core of PMT. Consequently, very concrete recommendations can be provided to change behavior and to alter programs when behavior change has not occurred (Kazdin, 2013a). Many treatment manuals and training materials for PMT are available for parents and therapists, only a small number of which can be noted (e.g., Barkley, 2013; Cavell, 2000; Forehand & Long, 2010; Kazdin, 2009; Kazdin & Rotella, 2008; McMahon & Forehand, 2005; McNeil & Hembree-Kigin, 2010; Turner, Markie-Dadds, & Sanders, 2010; Webster-Stratton, 2006). In short, information about implementing the treatment procedures is readily available. Also, Internet-delivered versions of PMT are available and appear to be effective, as initially studied in randomized controlled trials (e.g., Enebrink, Högström, Forster, & Ghaderi, 2012).

Several limitations of PMT can be identified as well. First, as with any treatment, not everyone responds. Second, PMT makes several demands on the parents, such as mastering educational materials that convey major principles underlying the program, systematically observing deviant child behavior and implementing specific procedures at home, attending weekly sessions, and responding to frequent telephone contacts made by the therapist. For some families, the demands may be too great to continue in treatment. Finally, perhaps the greatest limitation or obstacle in using PMT is that there are few training opportunities for professionals to learn the approach. Training programs in child psychiatry, clinical psychology, and social work are unlikely to provide exposure to the technique, much less opportunities for formal training. PMT requires mastery of social learning principles and multiple procedures that derive from them, but how to implement them is really critical, so learning about the techniques is not likely to be of much value (Cooper et al., 2007; Kazdin, 2013a).

Multisystemic Therapy

Background and Characteristics of Treatment. Multisystemic therapy (MST) is a family systems–based approach to treatment (see Henggeler, 2011; Henggeler et al., 2009). Family approaches maintain that clinical problems of the child emerge within

the context of the family and focus treatment at that level. MST expands on that view by considering the family as only one, albeit a very important, system. The child is embedded in multiple systems, including the family (immediate and extended family members), peers, schools, neighborhood, and so on. Also, within a given system, different subsystem issues may be relevant. For example, within the context of the family, some tacit alliance between one parent and child may contribute to disagreement and conflict over discipline between the parents. Treatment may be required to address the alliance and sources of conflict in an effort to alter child behavior. Child functioning at school may involve limited and poor peer relations; treatment may address these areas as well. Finally, the systems approach entails a focus on the individual's own behavior insofar as it affects others. Individual treatment of the child or parents may be included in treatment. Many different treatment techniques are used to address the multiple foci of the case. Thus, MST can be viewed as a package of interventions deployed with children and their families. Treatment procedures are used "as needed" to address individual, family, and system issues that may contribute to problem behavior. The conceptual view focusing on multiple systems and their impact on the individual serves as a basis for selecting multiple and quite different treatment procedures.

Several family therapy techniques (e.g., joining, reframing, enactment, paradox, and assigning specific tasks) are used to identify problems, increase communication, build cohesion, and alter how family members interact. The goals of treatment are to help the parents develop behaviors of the adolescent, to overcome marital difficulties that impede the parents' ability to function as parents, to eliminate negative interactions between parent and child, and to develop or build cohesion and emotional warmth among family members. MST draws on many other techniques as needed, such as PMT, problem-solving skills training, and marital therapy, to alter parent–child interactions at home, the response repertoire of the child, and marital communication, respectively. In some cases, practical advice and guidance are also given to address parenting issues (e.g., involving the adolescent in prosocial peer activities at school, restricting specific activities with a deviant peer group). Although MST includes distinct techniques from other approaches, it is not a mere amalgamation of them. The focus of treatment is on interrelated systems and how they affect each other. Domains are addressed in treatment (e.g., parent unemployment) if they raise issues for one or more systems (e.g., parent stress, increased alcohol consumption) and affect how the child is functioning (e.g., marital conflict, child-discipline practices). In any given case, multiple interventions are likely to be applied.

Evidence and Evaluation. A large number of randomized control trials have evaluated MST, primarily with delinquent and substance-dependent youths with arrest and incarceration histories including violent crime (Henggeler, 2011; Henggeler et al., 2009). MST is superior in reducing delinquency, drug use, and emotional and behavioral problems and increasing school attendance and family functioning, in comparison to other procedures, including "usual services" provided to such youths (e.g., probation, court-ordered activities that are monitored such as school attendance), individual counseling, and community-based eclectic treatment. Apart from the sheer number of controlled studies, the strength of this literature stems from the breadth of application across age groups and clinical problems.

Follow-up examinations have repeatedly supported the impact of treatment. For example, a 22-year follow-up showed reduction in arrests, adult confinement, and family instability (e.g., divorce, paternity, child support suits) following treatment of delinquency (see http://mstservices.com/proven-results/proven-results). A cost-benefit analysis by the Washington State Institute on Public Policy found that the effects of MST result in net monetary benefits (benefits of program minus cost of program) of approximately $32,000 per participant when considering only taxpayer benefits, and more than $132,000 when considering victim benefits along with taxpayer benefits (Aos, Phipps, Barnoski, & Leib, 2001; http://mstservices.com/proven-results/cost-effectiveness).

Moderators have been identified. For example, therapist adherence to the MST treatment protocol has been related to both improvements in family relations and decreases in delinquent peer affiliation, which, in turn, are associated with decreases in delinquent behavior. Therapist adherence to MST is influenced by referral type (lower ratings for youths referred for both criminal offenses and substance abuse relative to youths referred for either offenses or abuse); lower adherence is related to greater pretreatment arrests and school suspensions; and higher ratings are related to greater family educational

disadvantage and caregiver–therapist ethnic and gender match (Schoenwald, Halliday-Boykins, & Henggeler, 2003; Schoenwald, Letourneau, & Halliday-Boykins, 2005). A positive ethnic match (therapist and caregiver matched on ethnicity) is related to greater symptom reduction, greater length of treatment (i.e., more treatment retention), and increases in the likelihood of case termination due to the meeting of treatment goals (Halliday-Boykins, Schoenwald, & Letourneau, 2005).

There are several remarkable features of MST. First, many of the youths who are treated are quite severely impaired (delinquent adolescents with history of arrest). As part of evaluations of MST with such youth, social impact measures (e.g., rearrest, family problems, dropping out of school) have been studied in addition to the usual and more familiar psychological symptom outcome measures. Second, few evidence-based treatments have follow-up data in several studies, including the virtually unheard of 22-year follow-up of MST mentioned previously.

Third, and possibly the most salient feature, is the dissemination of MST. For a period spanning decades, MST has had mechanisms in place for extending treatment, training, consultation, and supervision (Henggeler, 2011; Henggeler et al., 2009; http://www.mstservices.com). This has led to application of MST throughout the United States and in several other countries. When agencies, organizations, and states want to adopt an evidence-based treatment, MST has been available with contracting and training mechanisms well in place. Add to that a key attraction, namely the effectiveness with severely disturbed populations. In the short term MST has surpassed the effects of psychiatric hospitalization, which has augmented the appeal of the procedure as hospital services and reimbursement for them have declined. Overall, the evidence base of MST is very strong, as attested to by multiple replications.

There remain important challenges for the approach. First, the administration of MST is demanding in light of the need to provide several different interventions in a high-quality fashion. Individual treatments alone are difficult to provide; multiple combinations of different treatments invite all sorts of challenges (e.g., therapist training, ensuring treatments of high quality, strength, and integrity). Second, and related, MST is intensive. In some projects, therapists are available 24 hours a day, 7 days a week. Sometimes a team of therapists is involved rather than merely one therapist. It may be the case that this model of treatment delivery is precisely what is needed for clinical problems that are multiply determined, protracted, and recalcitrant to more abbreviated interventions.

Overall, MST is an evidence-based treatment with excellent evidence on its behalf. The outcome studies have included youths with different types of problems (sexual offenses, drug use). Moreover, MST has been extended to many other problems (e.g., acute psychiatric crises; suicide attempts; depression, anxiety, and thought disorder), further supporting the viability of the model as a way of intervening for serious dysfunction. Moreover, as noted above, a model for dissemination and adoption has been in place for decades and hence the treatment is readily available.

Multidimensional Treatment Foster Care Model

Background and Characteristics of Treatment. Multidimensional Treatment Foster Care (MTFC) is a community-based treatment program (Forgatch & Patterson, 2010; Leve et al., 2012a,b; Smith & Chamberlain, 2010). It began as an alternative to institutional, residential, and group-care placements for youths with severe and chronic delinquent behavior and has since been extended to work with children and adolescents referred from either mental health or child welfare service systems.

The program provides opportunities for youth to live successfully in their communities while at the same time providing them with intensive supervision, support, and skill development, and to prepare their parents (or other aftercare resource) to provide effective parenting. (Approximately 85% of the youths return to their families; the remaining 15% return to long-term foster care or residential placement.) The youths begin treatment while they are out of their homes. They are placed individually in a foster home and are provided with intensive support and treatment in that setting. Individual placement is important and departs from many programs where several youths with antisocial behavior might be placed together in one setting. Evidence that group-based treatments for youth with CD can make them worse has fostered concern about many programs (e.g., Dishion, McCord, & Poulin, 1999; Mager, Millich, Harris, & Howard, 2005). Once the foster program is in place, PMT is provided to the parents (biological

or other) to whom the child will return after foster care placement.

In foster placement (e.g., 6 to 9 months), several interventions are provided, including family and individual therapy, skill training, academic support, case management, and medication, as needed. The interventions are provided across home, school, and the community. The foster setting is designed both to change the behavior of the youths and to prepare them for return to their families or placement in a different home. Four key elements of treatment provide youths with the following:

1. A reinforcing environment where they are mentored and encouraged to perform specific behaviors that will increase their skills;
2. Daily structure that includes clear expectations, limits, and consequences;
3. Close supervision and monitoring of the youth's whereabouts; and
4. Prosocial peer contacts and support rather than associations with delinquent peers.

Each child is supervised by a team including a case manager, individual therapist for the child, family therapist for the aftercare parents, behavioral support specialist, and psychiatrist, who conducts the treatment intervention. The team facilitates implementing and coordinating interventions, which take place across multiple settings (i.e., foster care setting where the child is placed, school, family home to which the child returns, and community). The overall conceptual focus of treatment is social learning—that is, providing learning experiences in the context of a positive interpersonal environment and various systems (home, community, school).

Foster parents are trained to implement behavioral programs and focus on such behaviors as getting up on time, attending school, positive behavior in class and at home, following directions, maturity, and positive attitude. Interventions are those that constitute PMT, highlighted earlier in the chapter (e.g., clear goals, feedback, praise, points, response cost). Parents to whom the child returns also receive PMT. They are gradually exposed to the child under supervision before the child is returned home to oversee the practices of the parents in light of their PMT. Parents visit the foster setting and the child visits the home of the biological parents. The gradual exposure to the home environment ensures that the transition will be smooth when the child is placed and that the biological parents have the skills and new ways of interacting to sustain gains in their child.

Evidence and Evaluation. Several randomized trials (type 1) have been completed with youth referred from multiple sources, including child welfare and mental health services, as noted previously (see Forgatch & Patterson, 2010; Leve et al., 2012a,b; Smith & Chamberlain, 2010, for reviews). The samples usually include individuals with comorbid disorders, a history of trauma and abuse, and prior treatments and multiple placements. Those with the most severe conduct problems have included youth referred from juvenile justice departments (aged 12 to 17), who have been involved in serious and frequent offending, and who are mandated by the courts for out-of-home placement.

The outcome studies have shown that the MTFC program leads to significant reductions in crime and delinquent behavior relative to treatment as usual. In the first outcome trial, delinquent youths were studied and randomly assigned to MTFC or treatment as usual (Chamberlain & Reid, 1998). In the case of chronically delinquent youths, treatment as usual consists of group-care placement, as determined by parole or probation officers. The program includes individual, group, and family therapy, although these can vary in conceptual approach and degree across settings. This initial study and by now the many others that have followed (e.g., Eddy, Bridges-Whaley, & Chamberlain, 2004; Eddy & Chamberlain, 2001; Leve et al., 2012b; Van Ryzin & Leve, 2012) conveyed the strong benefits of the MTFC program compared with control conditions. The benefits have been reflected on important outcome measures, including the extent to which youths run away, records and self-report of criminal activity, arrest rates, days spent in locked settings (e.g., state training schools), and reduced pregnancy rates among adolescent females (Smith & Chamberlain, 2010; Smith, Chamberlain, & Eddy, 2010). Follow-up studies have supported the effectiveness of MTFC up to two years (e.g., Chamberlain et al., 2007; Leve, Chamberlain, & Reid, 2005). The program has been extended to many other countries (Smith & Chamberlain, 2010).

Monetary costs of the MTFC program for treating individuals from the juvenile justice system are approximately one-third less than placement and treatment in group care (treatment as usual; Chamberlain & Smith, 2003). A cost-effectiveness

evaluation estimated that the MTFC model saves taxpayers approximately $44,000 per participant in criminal justice and avoids victim costs (Aos et al., 1999). For every dollar spent on MTFC, approximately $23,000 of taxpayer benefits were estimated when compared with more commonly used programs.

The evidence on behalf of the program is impressive in light of applications to severely impaired youth and extensions to multiple samples drawn from different types of agencies. Moreover, there have been several independent replications (e.g., Bolle et al., 2012; Farmer et al., 2010; Westermark, Hansson, & Olsson, 2011). The intensive effort required to implement treatment is noteworthy. For example, the team includes a case manager who can oversee more than one case (e.g., approximately 10 families). The case manager coordinates all facets of treatment. The demands can be great, as the manager provides daily telephone contact, supervises weekly foster parent meetings, and is available 24 hours a day. Yet, evidence-based programs for foster care are difficult to find. Moreover, the intervention has focused on children in great need (e.g., victims of child abuse, those in the child welfare system) and has produced quite favorable outcomes in relation to such critical indices as substance use, delinquency, depression, and teen pregnancy.

Overall, this is a well-developed program. It draws on two evidence-based treatment literatures. First, the evidence for this program is solid in its own right. This literature continues to emerge in replications extending to programs in many states in the United States and to other countries. Second, PMT is pivotal to the foster and biological parent facets of the intervention. The strong PMT literature, much of which has emanated from the same center (in Oregon) from which this intervention emerged, provides further evidence underpinning this treatment program (Forgatch & Patterson, 2010). Yet, the MTFC clearly has made its own contribution and findings beyond research on many of the constituent techniques. As one example, the effectiveness of MTFC was recently shown to be mediated by reducing peer associations with other delinquent youth (e.g., Van Ryzin & Leve, 2012), which is a novel addition for understanding how the intervention may work.

Cognitively Based Treatments

Background and Characteristics of Treatment. *Cognitive processes* refer to a broad range of beliefs, perceptions, attributions, and means of coding experience. Children and adolescents who engage in aggressive behavior show distortions and deficiencies in various cognitive processes. Several cognitive processes have been studied. Examples include generating alternative solutions to interpersonal problems (e.g., different ways of handling social situations); identifying the means to obtain particular ends (e.g., making friends) or consequences of one's actions (e.g., what could happen after a particular behavior); making attributions to others of the motivation of their actions; perceiving how others feel; and expectations of the effects of one's own actions (Larson & Lochman, 2010; Mayer et al., 2011). Deficits and distortion among these processes are typically reflected in teacher ratings of disruptive behavior, peer evaluations, and direct assessment of overt behavior.

As an example, aggression is not merely triggered by environmental events but rather through the way in which these events are perceived and processed. The processing refers to the child's appraisals of the situation, anticipated reactions of others, and self-statements in response to particular events. Attribution of intent to others represents a salient cognitive disposition critically important to understanding aggressive behavior. Children and adolescents with aggressive behavior tend to attribute hostile intent to others, especially in social situations where the cues of actual intent are ambiguous (e.g., Dodge, 2010; Werner, 2012). Understandably, when situations are initially perceived as hostile, children are more likely to react aggressively.

Although many studies have shown that children with CD experience various cognitive distortions and deficiencies, the specific contribution of these processes to CD, as opposed to risk factors with which they may be associated (e.g., untoward living conditions, low IQ), have not been established. Nevertheless, research on cognitive processes among aggressive children has served as a heuristic base for conceptualizing treatment and for developing specific treatment strategies (Kendall, 2011). Variations of cognitively based treatments have been applied to aggression and conduct problems. Arguably the most well developed and best documented are the Anger Coping Program and the Coping Power Program (Lochman et al., 2010). The Anger Coping Program is delivered in a group format in which themes (e.g., use of a puppet to model self-control, problem solving, perspective taking) is conducted. Core features

of this program are designed to alter how youth with aggressive behavior encode social situations and respond on the basis of that encoding. Cognitive training and practice of prosocial solutions and problem solving are central (see Lochman et al., 2010, for a detailed description).

The Coping Power Program involves an extension in the amount of treatment and has separate group sessions for the parents that focus on the home environment. Many of the group sessions with parents draw on PMT techniques (e.g., social reinforcement of target behaviors in the child, clear instructions). Interestingly, other researchers have combined cognitively based treatment for the child with PMT in part to support the changes in treatment but also to controvert many parenting practices that may promote aggressive behavior of the child (e.g., Kazdin, 2010; Webster-Stratton, Reid, & Beauchaine, 2011).

Another treatment variation is cognitive problem-solving skills training. This intervention has been applied clinically to inpatient and outpatient treatment rather than in the schools and has focused on children with CD as well as multiple other disorders (Kazdin, 2010). The emphasis is on how children approach situations—that is, the thought processes in which the child engages to guide responses to interpersonal situations. The children are taught to engage in a step-by-step approach to solve interpersonal problems. They make statements to themselves that direct attention to certain aspects of the problem or tasks that lead to effective solutions. Second, the behaviors (solutions to the interpersonal problems) that are selected are important as well. Prosocial behaviors are fostered through modeling and direct reinforcement as part of the problem-solving process. Third, treatment uses structured tasks involving games, academic activities, and stories. Over the course of treatment, the cognitive problem-solving skills are increasingly applied to real-life situations. Fourth, therapists play an active role in treatment. They model the cognitive processes by making verbal self-statements, apply the sequence of statements to particular problems, provide cues to prompt use of the skills, and deliver feedback and praise to develop correct use of the skills by the child. Finally, treatment usually combines several different procedures, including modeling and practice, role playing, and reinforcement and mild punishment (loss of points or tokens). Many of the core assumptions and processes of problem-solving skills training align with and directly overlap with those of the Anger Coping Program and Control Coping Program (e.g., involvement of the parents).

Evidence and Evaluation. Several controlled clinical trials (type 1 and 2) have been completed with children and adolescents with impulsive, aggressive, and antisocial behavior (see Lochman et al., 2010; Sukhodolsky, Kassinove, & Gorman, 2004, for reviews). Cognitively based treatments have significantly reduced aggressive and antisocial behavior at home, at school, and in the community. At follow-up, gains have been evident up to four years after treatment (Lochman et al., 2010). In general, the program has produced sustained effects and has prevented later antisocial behavior (e.g., marijuana and tobacco use).

The Anger Coping Program and the Coping Power Program have been very well evaluated and with multiple replications. Also, the applications have focused on school samples but have been extended to clinical settings as well. The program began with a child component, then encompassed a parent component, and finally moved to providing teachers with training. Problem-solving skills training has been evaluated in randomized trials but does not have the range of replications of the two other programs. It has been applied to inpatient and outpatient cases with severe conduct problems. In all of those applications the intervention is delivered on an individual rather than group basis.

The strength of the evidence in the context of treatment for referred cases stands on its own in support of cognitive problem-solving approaches. Yet, early development of the intervention began over three decades ago in the schools and in the context of prevention (see Shure, 1997, 1999). Application in the classrooms both in early and current versions of treatment provides an intervention outside of the usual mental health service settings. There are features of cognitively based treatment that make it an extremely promising approach. First, several controlled outcome studies have shown that it leads to therapeutic change. Second, the treatment has drawn on research on cognitive processes of children and adolescents with aggressive behavior and other conduct problems and has integrated that into effective treatment. Finally, and on a more practical level, many versions of treatment are available in manual form (e.g., Friedberg & McClure, 2002; Larson & Lochman, 2010; Lochman et al., 2008; Mayer et al., 2011; Sukhodolsky & Scahill, 2012).

As mentioned previously, group treatment programs for antisocial youth have often been found to produce negative outcomes, a finding attributed to the socialization and connection that group members have with peers who further foster antisocial behavior, in citations noted previously. Group Anger Control Training has not shown such effects: It does not lead to worse outcomes than no treatment, indeed just the opposite. This is encouraging and raises important questions about when and under what circumstances group processes and peer connections can be problematic.

The cognitively based treatments highlighted here focus on cognitive deficits and distortions often evident in children with aggressive and antisocial behavior. A key question is whether children can still gain from treatment even if they have few or no such cognitive deficits. This is analogous to the issue raised with PMT. Harsh and inept parenting is often associated with conduct problems, but PMT as a behavior-change intervention does not require that parenting practices be harsh to effect change in parents or children.

Functional Family Therapy

Background and Characteristics of Treatment. Functional family therapy (FFT) reflects an integrative approach to treatment that relies on systems, behavioral, and cognitive views of dysfunction (Alexander & Robbins, 2010; Sexton, 2011). Clinical problems are conceptualized from the standpoint of the functions they serve in the family as a system, as well as for individual family members. Problem behavior evident in the child is assumed to be the way in which some interpersonal functions (e.g., intimacy, distancing, and support) are met among family members. Maladaptive processes within the family are considered to preclude a more direct means of fulfilling these functions. The goal of treatment is to alter interaction and communication patterns in such a way as to foster more adaptive functioning. Treatment also is based on learning theory and focuses on specific stimuli and responses that can be used to produce change. Social learning concepts and procedures, such as identifying specific behaviors for change, reinforcing new adaptive ways of responding, and evaluating and monitoring change, are included in this perspective. Cognitive processes refer to the attributions, attitudes, assumptions, and expectations of the family. Family members may begin treatment with attributions that focus on blaming others or themselves. New perspectives may be needed to help serve as the basis for developing new ways of behaving.

The underlying rationale emphasizes a family systems approach. Specific treatment strategies draw on findings that underlie PMT in relation to maladaptive and coercive parent–child interactions. FFT views interaction patterns from a broader systems view that also focuses on communication patterns and their meaning. As an illustration of salient constructs, research underlying FFT has found that families of delinquents show higher rates of defensiveness in their communications, in both parent–child and parent–parent interactions, blaming, and negative attributions, and also lower rates of mutual support than do families of nondelinquents. Improving these communication and support functions is a goal of treatment.

FFT requires that the family see the clinical problem from the relational functions it serves within the family. The therapist points out interdependencies and contingencies between family members in their day-to-day functioning and with specific reference to the problem that has served as the basis for seeking treatment. Over the course of treatment, the family is encouraged to see alternative ways of viewing the problem; in doing so, the incentive for the family to interact more constructively is increased.

The intervention is administered across three reciprocal and interdependent phases (Sexton & Alexander, 2002). The first, engagement and motivation, has a primary aim of increasing the perception of the intervention's credibility within the family, which includes fostering an expectation of change and establishing the alliance between therapist and family members. This is accomplished, in part, through therapists' reframing negative themes of presenting problems into positive themes, to develop a family-focused perception of the maladaptive behaviors and emotions that may be present within the family. The second phase, behavior change, aims to identify targets of change for each family member, with the idea that changes are tailored to the unique characteristics of the family member, and are appropriate for the cultural and contextual underpinnings of the family. Foci of behavior change are expected to encompass cognitive, interactive, and emotional domains of functioning. The last phase, generalization, aims to apply the

changes observed in the second phase to other problem areas and/or situations in the family system. The primary goal in this phase is for treatment to foster the family's ability to maintain changes observed in treatment, and prevent relapses in dysfunction.

Evidence and Evaluation. Several controlled trials have evaluated FFT and have focused on populations that are difficult to treat, including adjudicated delinquent and multiple offender delinquent adolescents and adolescents who abuse drugs (see Alexander & Robbins, 2010, Sexton, 2011; Waldron & Brody, 2010). FFT has led to greater change than other treatment techniques (e.g., client-centered family groups, psychodynamically oriented family therapy) and various control conditions (e.g., group discussion and expression of feeling, no-treatment control groups). Treatment outcome is reflected in improved family communication and interactions and lower rates of referral to and contact of youth with the courts.

Research has examined processes in therapy to identify in-session behaviors of the therapist and how these influence responsiveness among family members (see Sexton, 2011). For example, providing support and structure and reframing (recasting the attributions and bases of a problem) influence family members' responsiveness and blaming of others. The relations among such variables are complex insofar as the impact of various type of statements (e.g., supportive) can vary as a function of gender of the therapist and family member. Evidence of changes in processes proposed to be critical to FFT (e.g., improved communication in treatment, more spontaneous discussion) supports the conceptual view of treatment.

Several noteworthy points can be made about FFT. First, the outcome studies indicate that FFT can alter conduct problems among delinquent youth who vary in severity and chronicity of antisocial behavior (e.g., youths with status offenses; others with multiple offenses and who have served in maximum-security wards; youths who have suffered trauma). For example, in one comprehensive evaluation, FFT was estimated to reduce arrests by 22.6% for program participants within one year (Taxy et al., 2012).

Second, cost-effectiveness analyses have shown FFT to surpass alternatives such as detention and residential treatment for delinquents (Sexton, 2011). The reduction of arrest rates alone has enormous cost benefits. Each averted arrest is estimated to prevent $51,600 in associated victim harms and other savings (Taxy et al., 2012), accounting for more than 60% of all savings from averted crimes.

Third, the evaluation of processes that contribute to family members' responsiveness within the sessions, as well as to treatment outcome, represents a line of work rarely seen among treatment techniques for children and adolescents. Some of this process work has extended to laboratory (analogue) studies to examine more precisely how specific types of therapist statements (e.g., reframing) can reduce blaming among group members (see Sexton, 2011). Fourth, details of treatments, including treatment manuals, have been provided (Alexander et al., 2013; Sexton, 2011); Internet sources also are available (www.fftinc.com/). Along with that there is a mechanism for large-scale dissemination that is in place and active. The Web site notes that, currently, "300+ community, state, national and international organizations . . . provide FFT to over 20,000 families each year."

On balance, the treatment has several features in its favor. The evidence includes many studies. The samples included in the studies have been severely impaired delinquent youth, including youth who have suffered trauma. As with other treatment packages reviewed in this chapter, it is not clear whether all the treatments that constitute the FFT "package" are needed or are needed for some, most, or all of the cases.

Brief Strategic Family Therapy

Background and Characteristics of Treatment. Brief strategic family therapy (BSFT) has emerged from a programmatic series of studies with Hispanic youths (see Robbins & Gonzalo, 2007; Robbins, Harigian, Szapocznik, & Ucha, 2010). The program has systematically evaluated children (aged 6 to 11), early adolescents (12 to 14), and adolescents (13 to 18) and included youths from varied backgrounds (e.g., Cuban, Nicaraguan, Colombian, Honduran, and Puerto Rican). Although the groups vary widely, the approach is based on the view that as a group Hispanics show more family orientation and shared values and many immigration and acculturation experiences that make the grouping meaningful. The youths have included those referred for externalizing behaviors such as CD, drug abuse, and a broader range of problems as well.

BSFT views child behavior within the context of the family system. Integrated into a family approach is a cultural frame of reference that draws from the study of Hispanic families. Among the key foci of this frame of reference are the importance of strong family cohesion, parental control, and communication issues that may arise from cultural and intergenerational conflicts (e.g., individualism of the adolescent vs. family ties). Both family and individual behavior are considered as interdependent and interactive. Individuals are jointly responsible for the state of the family system and for the changes that are to be made in treatment. Patterns of interaction, conceptualized as the structure of the family system, are identified as the likely bases for maladaptive functioning. Thus, a child's "problem" brought to treatment is reconceptualized as dysfunction in relation to the family. Persistent maladaptive behavior in one or more family members must in some way be maintained by the family.

Treatment focuses on strategies that can be used to alter interaction patterns. The focus is on providing concrete and direct changes in the family situation to promote improved interactions. This is distinguished from more traditional strategies that have focused on insight and understanding. The treatment sessions are problem focused whenever possible. The therapist identifies what can be altered within the family to promote change. Formal assessment is provided by a set of family tasks (e.g., planning a menu, discussing a prior family argument) that allow the therapist to identify areas of focus. Structure of the family, alliance, conflict resolution, roles (e.g., patient, model child), and flexibility of the family are some of the dimensions that are examined in assessment and focused on in treatment. During treatment, the therapist challenges interaction patterns, reformulates (reframes) ways of considering interaction and communication patterns, and encourages new ways of interacting to break up established sequences.

Evidence and Evaluation. There have been many randomized controlled trials to develop and evaluate the intervention with youths referred for diverse problems. The results have shown improvements in child and family functioning as a result of treatment when compared with other treatment and control (e.g., minimal contact conditions) across several studies (see Robbins et al., 2010; Rowe, 2012). The benefits are reflected in reductions in parent-reported conduct problems and delinquency, substance use, and improved family functioning. Although the outcome focus of treatment emphasizes child and adolescent behavior, changes in the family are viewed as critical as well. Comparisons early in this program of research showed that even when two interventions (BSFT and psychodynamic therapy) were equally effective in reducing symptoms, BSFT also improves family functioning (Szapocznik et al., 1989).

Among the strengths of the program are efforts to engage the family in order to retain them in treatment (Ingoldsby, 2010). Special attention to the family early in treatment that addresses family and cultural barriers to treatment participation has been evaluated in randomized controlled trials; it significantly reduces dropping out of treatment. The engagement procedure and remaining in treatment, as might be expected, relate to treatment effectiveness.

Overall BSFT has been studied in a well-developed program of research. Treatment has been replicated in several studies and with children presenting diverse clinical problems. The research program is unique in directly developing a treatment sensitive to critical cultural issues and developing methods to assess these issues. The program has been extended to African American families and to other clinical problems than conduct problems (e.g., substance use, prevention of HIV). Apart from the accomplishments of the studies in relation to BSFT, the broader approach of assessing and studying cultural features of families and then integrating these features into therapy may reflect a model for developing ethnically relevant and sensitive treatment. There has been relatively little attention to ethnic issues in trials of psychotherapy with children and adolescents, and this program has been exemplary.

Good Behavior Game

Background and Characteristics. The interventions mentioned so far are within the realm of traditional models of psychotherapy in the sense of providing therapy in the context of treatment to individuals or to families. An exception is one of the cognitive therapy programs that has been routinely conducted in the schools. Another exception is PMT, which has been extended to schools to deliver the intervention to parents or to adopt the interventions for teachers. Other interventions have emanated from classroom applications and have strong evidence on their behalf as an intervention for aggressive behavior.

A classroom-based intervention referred to as the Good Behavior Game (GBG) has been effective for children with aggressive behavior. The class is divided into two (or more) teams. Classroom rules are posted that identify the target behaviors and reinforcers. When one of the rules is violated (e.g., talking out, hitting another person) the student is noted by name and the violation is stated specifically. The rule infraction leads to a loss of points from the team's total points. This loss can be noted by a point on a board or loss of a point—some public way of designating or tracking the number of infractions. At the end of the day and of the week, the team with fewer infractions earns a prize (e.g., could be a tangible reinforcer, a privilege, and praise as special recognition by the other team). Among the advantages of the system is the team competition, which adds an incentive to the usual group program. Essentially, this is a two-group program in one classroom and the two groups are in competition for which can behave better.

The principles underlying the program are based on those of applied behavior analysis, including reinforcement, mild punishment, careful specification of the target behaviors, and others (see Kazdin, 2013a). These principles and practices derived from them include many of the practices that underlie PMT and MTFC, highlighted previously. Thus, support for the intervention can draw from many other applications both for CD and other problem domains.

Evidence and Evaluation. The GBG has been used in elementary through high-school classrooms, in regular and special education classes, and with ethnically diverse samples (see Embry, 2002; Kleinman & Saigh, 2011; Tingstrom et al., 2006). In the typical study, the GBG is used as a strategy to help teachers manage classroom behavior and promote academic behavior. Many studies have demonstrated this use of the GBG with individual classrooms. However, in various applications the GBG has been extended to a large number of classrooms across several different schools, with impact on academic performance and disruptive behaviors (e.g., Dion et al., 2011; van Lier et al., 2004).

Multiple studies have attested to the effectiveness of the program in reducing aggressive behavior and improving classroom performance (e.g., attentive behavior, perseverance on tasks) while the program is in effect. Especially remarkable have been the follow-up results. When the program is implemented in early elementary school (first and second grades) the impact can be seen years later.

For example, a large-scale evaluation (e.g., first graders in 41 classrooms in 19 schools in Baltimore, Maryland) included multiple randomized trials to test the impact of early school intervention on later outcomes when the youth were aged 19 to 21 (Kellam et al., 2008; Poduska & Bowes, 2010). The impact of GBG relative to regular classrooms or regular classrooms with special reading achievement programs was remarkable. GBG youth, especially males who were more aggressive and disruptive in early grades, showed reduced rates of: drug and alcohol abuse and dependence, cigarette smoking, use of special school services (e.g., for problems with behaviors, drugs, alcohol), violent and criminal behavior; antisocial personality disorder, and suicide ideation and attempt. The effects have been replicated in other large-scale applications (Leflot et al., 2010, 2013).

Overall, the GBG has been shown to decrease behaviors such as aggression and classroom disruption and apparently interrupt the path to which these can lead for many children in terms of substance use and abuse and the other outcomes noted previously. The research, only highlighted here, conveys that the GBG can be used as a treatment (for the immediate effects) and preventive intervention for children with aggression and disruptive behavior for a host of untoward outcomes in adolescence and young adulthood. By implementation in the schools this can be used on a large scale (multiple classrooms and schools) and for treatment and prevention.

General Comments

I have highlighted several evidence-based treatments for youth with conduct problems. The treatments encompass young children through adolescents and a range of severity from oppositional and noncompliance to serious antisocial and criminal behavior. The research has included youths referred clinically, as well as from the courts, child welfare and protective services, and various agencies where such children may reside (e.g., foster care). Occasionally, critical evaluations of evidence-based treatments note that perhaps the participants are not like "real" patients referred for treatment, or perhaps they do not have serious or multiple disorders. Plainly the concern is incorrect in relation to evidence-based treatments

of CD. The treatments (e.g., PMT, MST, MTFC) include cases with all sorts of serious child, parent, family, and social problems. In terms of psychiatric diagnosis, our own studies show that comorbidity is the rule rather than the exception in our trials, with some children meeting criteria for five or six psychiatric disorders and that treatment is effective nevertheless (e.g., Kazdin & Whitley, 2006).

There are now multiple treatments available for youth with CD. Extending these to professionals and families in need is not the only task remaining, as I note in the sections that follow, but it is likely to be the most daunting. I have focused on the treatments that have been well established for some time (e.g., between three and five decades). More recent evidence makes the case stronger. Add to this that the cost and cost-benefits of the treatments have been quite favorable, and we can make the case that these treatments do not only "work" but are also worthwhile investments. Even so, there remain multiple issues regarding the impact of treatments and their dissemination.

CRITICAL ISSUES IN EVALUATING TREATMENTS

The treatments highlighted in the chapter have randomized controlled trials (type 1) on their behalf, including replications of treatment effects. The treatments encompass young school-age children through older adolescents and a range of youths varying in severity of aggressive and antisocial behavior (oppositional, CD, adjudicated delinquent and repeat offenders) and as included in or referred from various agencies (e.g., clinics, hospitals, courts). Some of the treatments have long-term follow-up (e.g., more than 20 years), which is rare across the full range of psychosocial therapies. The main conclusion is worth underscoring: *There are now several evidence-based treatments for conduct disorder.*

Interpretation of Findings of Evidence-Based Treatments

There are qualifiers about what we know and what can be said about evidence-based treatments that certainly apply to those related to CD. No single definition or set of criteria has been used to designate treatments as evidence-based. Several countries, professions, organizations within professions, and other parties (e.g., third-party payers; state, provincial, and federal governments) have delineated evidence-based treatments with varying criteria. Even so, commonly used criteria are that the treatment has been studied in randomized controlled trials, it has been shown to be more effective than another condition (e.g., no treatment, treatment as usual), and these effects have been replicated, preferably by independent research teams. "More effective" means that the treatment condition was statistically better than a control group. Often effect sizes complement tests of statistical significance to convey the magnitude of the relation between treatment and therapeutic change.

It is important to bear in mind that neither statistical significance nor effect size (even if large) has any necessary connection to the clinical or practical importance of the therapeutic change. It is easy to show that statistically significant differences between groups and large effect sizes can be readily obtained with little or no clinical benefit (Kazdin, 2013b). Thus, the clinical utility of evidence-based treatments and their superiority over other conditions (e.g., treatment as usual) are not so clear. The significance of this latter point is hardly trivial. In addition to knowing which treatments lead to greater therapeutic change than many control conditions, we must also understand whether and how this translates to client functioning in everyday life.

In some of the treatments I have reviewed (e.g., MST, MTFC, GBG), outcomes include social impact measures such as school dropout, rearrest, readjudication, hospitalization, days of confinement, criminal behavior, and pregnancy rates. These measures have clear practical referents in relation to the impact of treatment. It is likely that changes on these measures reflect palpable changes in children and adolescents and hence are "clinically significant." Such measures raise a related concept that might be referred to as "socially significant." I refer to social significance as a measure in which some meaningful outcome of broad interest to society (e.g., cost, use of resources) is affected by the treatment. Clearly more is needed in evaluating treatments for CD that establish palpable changes in the children and families and in the social impact of treatment. Yet, already, measurements in support of the techniques include but go beyond symptom ratings.

Another issue that qualifies interpretation of evidence-based treatments pertains to how the studies are reported. Typically, studies use multiple measures to evaluate therapeutic change. Frequently, some measures show the predicted differences in support of the treatment, whereas other measures do not. Researchers often consider the former to support the effectiveness of treatment, yet the measures that do not show the treatment effect often are excluded or minimized when drawing conclusions (see De Los Reyes & Kazdin, 2006). That is, there has been great inconsistency among investigators in reporting criteria in which measures are not all considered or specified in advance as primary or secondary measures.[3] The implication for rendering conclusions across many studies is not knowing which indicators have changed and which have not and, most importantly, what conclusions could be drawn if all available measurement data were considered.

These concerns illustrate some of the ambiguities regarding the interpretation of evidence-based treatments. However, this is not grounds for abandoning or dismissing these therapies in clinical practice. In many instances, as I have mentioned, these treatments have been shown to make a difference and to surpass the gains achieved through usual or more traditional interventions. Yet, the qualifiers about what we can say about these treatment are not minor; further research is needed to redress them.

Dissemination of Evidence-Based Treatments

Developing effective interventions does not mean they will be adopted or used in clinical practice. Even when techniques are used in clinical practice, their effectiveness drops sharply from what the results show in controlled treatment studies (see Wampold et al., 2011; Weisz, Ng, & Bearman, 2014). Beyond concerns regarding the fidelity of treatment application, the vast number of treatments now available means that the task of extending even a small set of these to a clinic or set of therapists is enormous. Moreover, most training programs (e.g., graduate work in clinical psychology or social work; residency training in psychiatry and child psychiatry) are not likely to include evidence-based treatments as part of course work, let alone supervised training and mastery of them. Finally, dissemination is not merely a matter of discussing treatment, completing a continuing education experience, or seeing the treatment in action: Many evidence-based treatments involve specialized knowledge and skill sets.

Providing the requisite training and experience is a formidable challenge. Possible solutions have been advanced (see Chorpita & Daleiden, 2010; Shafran & Craske, 2009; Weisz et al., 2014). These include identifying components of treatments or modules that can be more readily used than all the individual evidence-based treatments, developing unified treatment protocols for treatments that have impact across a diverse range of disorders, training many nonprofessionals on a national scale (e.g., United Kingdom) to address a few but highly prevalent clinical problems (e.g., depression and anxiety), developing research that begins with clinical practice settings rather than research settings, and providing training and certification in highly specialized interventions (e.g., behavior analysis, dialectical behavior therapy, PMT).

An excellent example of a novel way of providing treatment is providing one or more of three evidence-based modules to children referred for diverse clinical problems in outpatient services (Weisz et al., 2012). The modules included cognitive-behavioral therapy for depression, cognitive-behavioral therapy for anxiety, and behavioral parent training for conduct problems. Modules were provided as needed depending on the problems of the children. A comparison condition of treatment as usual was also included. The program included children with multiple and comorbid disorders, including CD. The results showed the benefits of a modular approach on symptoms and impairment at the end of treatment. The benefits of treatment on symptom scores were maintained at a two-year follow-up (Chorpita et al., 2013).

The model of providing treatment in modular form may greatly enhance the dissemination of evidence-based treatments. A small set of modules are likely to be applicable with a large range of clinical problems. Also, with a limited number of modules, rather than a long list of treatments, training clinicians in practice is much more feasible.

RESEARCH PRIORITIES AND FUTURE DIRECTIONS

Several topics are high priorities for research. In some cases the research foci are not new but the approaches used to address them are.

Moderators

Moderator refers to some characteristic that influences the direction or magnitude of the relation between the intervention and outcome. If treatment outcome varies as a function of characteristics of the child or therapist (e.g., sex, ethnicity, temperament, biomarkers) or treatment delivery (e.g., individual vs. group treatment), these characteristics are moderators. Historically, the dominant question that has guided psychotherapy has been about moderators, as illustrated by, "What treatment, by whom, is most effective for this individual with that specific problem, under which set of circumstances?" (Paul, 1967, p. 111). The question continues to receive prominence as the treatment agenda to guide research (e.g., Roth & Fonagy, 2005).

After decades of study, the literature is saturated with moderators for CD, but we rarely understand why they moderate, and it is nearly impossible to translate the findings to assign people to treatments for which they are well suited. For example, socioeconomic disadvantage and severity of conduct problems moderate the effects of treatment for CD (e.g., Kazdin, 2010; Leijten et al., 2013). Individuals with greater socioeconomic disadvantage, family stress, and severity of dysfunction respond less well to PMT. However, these findings on moderators of treatment do not help in relation to theory, research, or practice because we do not know whether the moderator is specific to a particular technique or would apply to any other evidence-based therapy. Also, without knowing why the moderator has an effect, there is not much we can do to controvert the process or influence the means by which the moderator exerts its effect. In the absence of further explanation, moderator research to date has not advanced our understanding of the underpinnings of treatment effects, nor has it been especially useful for selecting among treatments for CD.

Two lines of moderator research may point the way to future advances. First, efforts to understand moderators and how they relate to fundamental features of information processing may hold special promise. For example, biological features of how patients process information (e.g., neuromarkers) and psychological characteristics with which they are associated (e.g., processing social cues, working memory, emotion regulation) serve as moderators of treatment response (psychotherapy, medication) (e.g., Doehrmann et al., 2013; Furey et al., 2013). These moderators can relate to fundamental biological features of disorders and elucidate targets for psychosocial and biological treatments. Such work also has the potential of elaborating unifying processes across diverse treatments.

Second, the ways in which moderators are studied are likely to change in the coming years. Moderators (e.g., severity of dysfunction, comorbidity, culture) usually are studied one at a time in any individual study. Individual moderators tend to be weak in how they predict outcome (e.g., effect size) and may not emerge as statistically significant, even when they exert practically significant influences on treatment–outcome relations. Recently, methods for integrating and combining multiple moderators have been elaborated (Kraemer, 2013). When multiple moderators are combined, moderator × treatment interactions emerge that otherwise would not be evident (e.g., Frank et al., 2011; Wallace et al., 2013).

Improvements in moderator research are greatly needed to advance clinical practice and decision making. Few studies are theoretically driven to predict how and why moderators operate. In addition, it has been difficult to direct patients to treatments from which they are very likely to profit and away from those from which they are not. Therapy research would profit from selecting and evaluating moderators in ways that translate to better care.

Mediators and Mechanisms of Change

Notwithstanding the rich outcome literature, we have very little idea about how treatments "work" or lead to change. Without understanding how therapeutic change is achieved, we are at a disadvantage in knowing how we might optimize change through activation of specific components or processes. Research on mediators and mechanisms underlying therapeutic change aims to elaborate how treatment works.

Mediator is a construct that shows a statistical relation between an intervention and outcome. This is an intervening construct that suggests processes about why change occurs or on which change depends. Mediation is evident when several conditions are met: (1) the intervention leads to change in outcome measures, (2) the intervention alters the proposed mediator, (3) the mediator is related to outcome, and (4) outcome effects are not evident or significantly (statistically) less evident if the mediator did not change.

These relations convey that change was mediated (e.g., correlated with, depended on) by some construct. Even when these conditions are met, ambiguity can remain about the precise role of the mediator (Bullock, Green, & Ha, 2010; Kazdin, 2014). The mediator may not, and usually is not intended to, explain precisely how the change comes about. For example, cognitions may be shown to mediate change in therapy; however, this does not explain precisely how the change came about (i.e., what are the intervening steps between cognitive change and reduced stress or anxiety).

Mechanism refers to a greater level of explanatory specificity than mediator and reflects the steps or processes through which therapy (or some independent variable) actually unfolds and produces the change. Mechanism explains how the intervention translates into events that lead to the outcome or precisely what was altered that led to symptom change.

Psychotherapy research with adults outside of the context of treatment of CD in children has benefitted from advances in cognitive, affective, and social neuroscience, as well as the development of noninvasive neuroimaging and other biological assays to examine the structure, function, and activity of the brain that are associated with clinical dysfunction (especially anxiety and depression) and/or changes over the course of psychotherapy among adults (e.g., Frewen, Dozois, & Lanius, 2008; Porto et al., 2009; Quidé, Witteveen, El-Hage, Veltman, & Olff, 2012; Roffman et al., 2005). Much of this work, but certainly not all, is correlational when characterizing disorders or change processes. Yet, the strength of the research stems from multiple lines of converging evidence that move closer to identifying mechanisms of action. For example, from the reviews mentioned previously, research has

- Identified neurological characteristics associated with specific disorders and subtypes;
- Evaluated change in neural processes in "regions of interest" in light of characteristics associated with specific disorders;
- Induced or provoked symptoms (e.g., sadness manipulations in healthy samples; trauma stimuli in posttraumatic stress disorder patients) to demonstrate experimentally brain areas implicated in dysfunction;
- Demonstrated "normalization" of neurological structures, function, and activity after therapy is completed;
- Elucidated similarities and differences in specific brain processes altered by different interventions (e.g., medication, psychotherapy) for a given disorder (e.g., major depression); and
- Documented some similarities in what brain processes are altered by the same intervention (e.g., cognitive-behavioral therapy) as applied to different disorders (e.g., obsessive-compulsive disorders, depression).

Neuroimaging studies capitalize on a set of tools to elaborate processes involved in therapeutic change. Additional methods have been used to study brain receptors, intracellular signaling, and target genes that reflect dysfunction and change over the course of treatment (e.g., Duman, Schlesinger, Russell, & Duman, 2008; Sen, Duman, & Sanacora, 2008). Capitalizing on novel methods of assessment may help in identifying processes that change over the course of effective intervention as well as suggesting biomarkers that moderate treatment effects.

A clear research direction and priority will be elaborating biological changes that underlie and are associated with changes in symptoms, behaviors, and subjective experience. There is a concern that drawing on advances in neural assessment methods unwittingly will contribute to the "biologizing" of psychotherapy (i.e., reverting to biological and "reductionist" explanations). However, core psychological and biological processes increasingly are studied together (e.g., cognitive, social, and cultural neuroscience) to elaborate the connections, reciprocal relations, and conversions of experience and brain processes.

Transdiagnosis and Transtreatment

Developing evidence-based therapies has focused on matching treatments to specific dysfunctions. Psychiatric diagnosis has served as the basis for this and of course harbors the view that there are discrete entities (syndromes and disorders) such as CD, oppositional defiant disorder, major depression, bipolar disorder, and a few hundred more (e.g., APA, 2013; World Health Organization [WHO], 2010). Treatments were (and continue to be) developed with a disorder focus. Yet, an alternative view, referred to as transdiagnosis, has taken hold as a novel model for understanding clinical dysfunction, underlying

processes, and treatment. Transdiagnosis refers to the study of processes that span many different manifestations of clinical dysfunction (e.g., Harvey, Watkins, Mansell, & Safran, 2004; Kring & Sloan, 2009).

Several factors have served as impetus for a transdiagnostic conceptualization of clinical dysfunction. Among the key interrelated influences are findings that

- There are high rates of comorbidity so that individuals (children or adults) who meet criteria for one disorder are likely to meet criteria for at least one other disorder as well (e.g., Kessler et al., 1994; Wichstrøm et al., 2012);
- Underlying processes that maintain "different disorders" often are quite similar (e.g., Fairburn, Cooper, & Shafran, 2003; Green et al., 2010; Jagannath, Peirson, & Foster, 2013);
- Several disorders share common biological underpinnings as reflected in brain structures, neurotransmitters, and genes (e.g., Meyer-Lindenberg & Tost, 2012; Smoller et al., 2013);
- A number of evidence-based treatments (e.g., cognitive-behavioral therapy, mindfulness) are effective across a range of disorders, suggesting some common mechanisms or core processes (e.g., working memory, emotion regulation) (e.g., Johnston et al., 2013); and
- Broad characteristics such as a general psychopathology factor (a "p factor"), neuroticism, perfectionism, and tolerance of uncertainty might serve as underlying or mediating characteristics of many different disorders (Barlow et al., 2014; Caspi et al., 2014; Egan, Wade, & Shafran, 2011; McEvoy & Mahoney, 2012).

These findings have inspired efforts to search for core psychological (e.g., working memory, cognition), environmental (e.g., exposure to trauma, violence, parent with depressed affect), and biological processes (e.g., neuromarkers, genetic), and their interrelations (e.g., epigenetic) that unite several types of clinical dysfunction that have been viewed as discrete diagnostic entities. Budding efforts to focus diagnosis on core psychological and biological processes also are emerging in new diagnostic work that may inform disorders from a transdiagnostic perspective (e.g., Cuthbert & Insel, 2013).

Transdiagnostic conceptualizations have altered treatment and treatment research. Rather than adding to burgeoning lists of treatments for specific disorders, attention is now being directed to the search for transdiagnostic treatments. Terms such as transdiagnostic treatment, unified treatment protocol, and unified cognitive-behavior therapy are increasingly evident in treatment literature (e.g., Allen, McHugh, & Barlow, 2008). It is likely that research will continue to explore treatments that are broad in applicability across diverse disorders. As an example related to this chapter, PMT for decades has been used to treat conduct problems (externalizing behavior). Yet, the treatment has been successfully extended to quite different disorders (e.g., anxiety disorders, autism spectrum disorders). Transdiagnostic/transtreatment thinking no doubt will expand to address what we can treat effectively with what we know.

Reaching Children and Families in Need

The scope and impact of psychological dysfunction, whether conceived from a disorder-specific or transdiagnostic perspective, are extraordinary. Among children, adolescents, and adults, 20% to 25% of community samples meet criteria for at least one psychiatric disorder. Prevalence alone does not convey the burden to individuals or society. Mental disorders are more impairing than common chronic medical disorders, with particularly greater impairment in the domains of home, social, and close-relationship functioning (Druss et al., 2009).

A critical aspect to reducing the burden of mental illness is the ability of effective interventions to reach those in need of services. Recent years have seen an increase in the proportion of people in need who receive treatment in the United States, from 20.3% of individuals suffering from a disorder receiving treatment (e.g., psychiatry services, complementary and alternative medicine) between 1990 and 1992 to 32.9% of individuals with a psychiatric disorder receiving some form of treatment between 2001 and 2003 (Kessler et al., 2005). Despite these gains, 70% of individuals who need services are not receiving them. Ethnic disparities with respect to access to mental health care add important challenges to providing services. Ethnic minority groups (e.g., African, Hispanic, and Native Americans) have much less access to care than do European Americans (e.g., McGuire & Miranda, 2008; Wells, Klap, Koike, & Sherbourne, 2001). The lack of available services for most people and systematic disparities among those

services that are available underscore the importance of delivering services in ways that can reach many more people while targeting (and likely responding to the unique needs of) special groups.

The dominant model of delivery across varied therapy techniques is administration by a highly trained (e.g., master's or doctoral level) mental health professional in one-to-one, in-person sessions with a client who visits a particular setting (e.g., clinic, private office, health care facility). This is referred to as the dominant model because clinical practice, graduate training, clinical program accreditation, pre- and postdoctoral internships, and research on psychosocial interventions draw heavily on this model. The one-to-one, in-person model is enduring, in demand, and suitable to deliver many treatments to individuals and families who access them. With the exception of the school-based treatments I mentioned, most evidence-based therapies for CD (and other disorders) are delivered via this traditional model.

Within the mental health professions, models of delivering psychosocial interventions are expanding. Many of these involve the use of technology and online versions of treatment that draw on the Internet and other media, including video, phone, and application software (apps) for smartphones and tablets. Some uses of technology are variants of the dominant model in the sense that they are one-to-one and face-to-face programs (e.g., individual sessions by webcam) but extend to places where there may be no service or suitable facilities available (e.g., Wooton, 2003). Other extensions include self-help interventions and a vast array of techniques (e.g., online interventions, expressive writing techniques) that are available 24/7 and require little or no assistance from a trained professional (L'Abate, 2007). Several Internet, computer-based, self-help, and low-cost psychological interventions are evidence based and achieve effects (i.e., effect sizes) at least on par with the similar technique administered in person by a trained mental health professional, and are high in client adherence to and satisfaction with treatment (e.g., Andrews et al., 2010; Cartreine, Ahern, & Locke, 2010; Harwood & L'Abate, 2010).

Novel models of delivery are needed that include but go well beyond the use of technology. Models are needed that have such characteristics as

- Reach: Capacity to reach individuals not usually served or well served by traditional service delivery models;
- Scalability: Capacity to be applied on a large scale or larger scale than traditional service delivery;
- Affordability: Relatively low cost compared to the usual model that relies on individual treatment by highly trained (master's, doctoral degree) professionals;
- Expansion of nonprofessional workforce: Increase the number of providers who can deliver interventions;
- Expansion of settings where interventions are provided: Bring interventions to locales and everyday settings where people in need are likely to participate or attend already; and
- Feasibility and flexibility of intervention delivery: Ensure the interventions can be implemented and adapted to varied local conditions to reach diverse groups in need.

Several such models have emerged from global health care, from business models of delivering innovations, and from nontraditional forms of interventions for mental health treatment (see Kazdin & Rabbitt, 2013). As one illustration, task shifting is a method of strengthening and expanding the health care workforce by redistributing the tasks of delivering services to a broad range of individuals with less training and fewer qualifications than traditional health care workers (e.g., doctors, nurses) (see WHO, 2008). Task shifting is an evidence-based model of delivery that has been used extensively in treating and preventing physical disease but also has been extended to treat psychiatric disorders (e.g., anxiety, depression, schizophrenia) (e.g., Balaji et al., 2012; Patel et al., 2010; Rahman et al., 2008).

Research has focused almost exclusively on evidence-based *treatments*. In the coming years, much greater priority is likely to be given to evidence-based *models of delivery*. It is obvious we have many interventions that simply cannot get to the people in need. Even broad treatments (e.g., transdiagnostic treatments) and dissemination of current treatments to clinicians in practice will not have a palpable effect on reducing the burdens of mental illness until we can take these efforts to scale. We still need to attend to evidence, of course, but we must direct our attention to evidence that supports interventions that can be effective, can be administered on a large scale, and can reach many unserved segments of the populations in need (see Kazdin & Blase, 2011; Kazdin & Rabbitt, 2013).

CONCLUSION

The development of evidence-based treatments for aggression and antisocial behavior in children and adolescents is a major advance. There are effective interventions for CD and for a broad spectrum of disruptive behaviors, including oppositional defiant disorder, CD, and delinquent behaviors. Still, it is surprising how little we know about how treatments actually achieve the changes that are now well demonstrated. In the coming years, key issues that are likely to receive major attention include

- Disseminating and evaluating treatment in clinical practice settings;
- Identifying common ingredients or transdiagnostic treatments that may not only facilitate dissemination but also establish a new way to conceptualize interventions and clinical dysfunction;
- Elaborating moderators of treatment that can be clinically useful and guide decision making;
- Elucidating the mechanisms through which therapeutic change occurs; and
- Scaling up our interventions to reach people in need of services.

The notion of translational research from medicine captures broadly key issues and priorities for therapy research in the coming years. Translational research focuses on "bench to bedside" (i.e., laboratory to clinical application) and also "bedside to community" (i.e., scaling up interventions to have impact). Extending treatments to practice and communities on a larger scale increasingly will serve as points of departure for developing interventions. We now have several evidence-based treatments for conduct problems, and perhaps armed with that the challenges involved in having those in need actually receive them are more salient than ever.

NOTES

1. *Children* will be used to refer to both children and adolescents. When pertinent to the discussion, a distinction will be made and referred to accordingly.

2. This section provides only an overview of the treatments presented. The treatments are the topic of reviews and book chapters, books, and treatment manuals, as referred to in the treatment descriptions and references to other sources.

3. There has been increased concern about selective reporting of measures and how this can bias the conclusions in psychological research more generally outside the context of intervention research (Simmons, Nelson, & Simonsohn, , 2011). To combat this in the context of treatment, funding agencies (e.g., National Institutes of Health), organizations (e.g., World Health Organization) and a consortium of journal editors (the International Committee of Medical Journal Editors) require individuals to register their clinical trials in advance of the study. Investigators complete information to convey exactly what the measures are, what the primary measures will be, and how the measures will be examined. ClinicalTrials.gov in the United States is the largest clinical trials database, and as of this writing over 140,000 studies have been registered; they encompass all fifty U.S. states and 183 countries (http://clinicaltrials.gov/). As investigators are required to specify and prioritize outcomes in advance, interpretation of the effects of treatment ought to be enhanced.

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6

Pharmacological Treatments for Schizophrenia

Atheir I. Abbas
Jeffrey A. Lieberman

Schizophrenia is a chronic mental disorder with a lifetime prevalence rate of approximately 1%. The first antipsychotic drug, chlorpromazine, was introduced in 1954, followed by several similar drugs. With the later introduction of clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and more recently paliperidone, iloperidone, asenapine, and lurasidone, antipsychotic drugs are often classified as first-generation or typical (chlorpromazine-like) versus second generation or atypical (clozapine-like), although the distinction between the two classes, particularly with respect to efficacy, is not as meaningful as had initially been believed. Both of these broad classes of medications have been demonstrated to safely improve psychotic symptoms in the acute phase of the illness and reduce risk of relapse in the maintenance phase of treatment. Because of the limited efficacy of antipsychotic medication in resolving the full range of schizophrenic psychopathology, adjunctive treatments are often used to reduce morbidity. Concomitant medications such as benzodiazepines, lithium, carbamazepine, valproic acid, antidepressants, glutamate agonists, and dopamine agonists have been used alone and in combination with antipsychotic drugs to improve treatment response. In this chapter, we review controlled trials of the pharmacological agents used to treat schizophrenia.

BACKGROUND

According to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* 5 (*DSM-5*), clinical diagnosis of schizophrenia is dependent on the presence of two of the following five symptom domains: delusions; hallucinations; disorganized speech; grossly disorganized or catatonic behavior; and negative symptoms such as avolition, blunted affect, impoverished speech, and anhedonia, with 6 months of continuous disturbance and symptoms that meet full criteria for at least 1 month, or less if successfully treated. These symptoms must take place in the presence of significant social and occupational impairment that often precedes the diagnosis for some years. A few changes have been made in the *DSM-5* compared to *DSM-IV-TR*, largely due to issues of specificity, reliability, and/or validity. First, there is now a firm requirement for two Criterion A symptoms, eliminating the possibility of a diagnosis of schizophrenia with just the presence of bizarre delusions or Schneiderian first-rank auditory hallucinations (two or more voices conversing). Also, at least one of three core positive symptoms of delusions, hallucinations, or disorganized speech must be present to diagnose schizophrenia. Notably, the *DSM-IV* subtypes of schizophrenia have been eliminated due to their limited diagnostic stability, low reliability, and poor validity. Other changes to the chapter on schizophrenia spectrum disorders include the requirement for schizoaffective disorder that a major mood episode be present for a majority of the disorder's total

duration after Criterion A has been met, the elimination of the requirement that delusions in delusional disorder be non-bizarre, and changes to the way catatonia is diagnosed.

Schizophrenic psychopathology has been characterized as divided into three symptom clusters: positive symptoms composed of delusions, hallucinations, and disorganization; negative symptoms such as anhedonia and avolition; and cognitive symptoms such as impairments in executive functioning, working memory, and attention (Liddle, Carpenter, & Crow, 1994). Approximately 75% of patients with schizophrenia have clinically meaningful deficits in at least two cognitive domains, and 90% have deficits in at least one domain (Palmer et al., 1997). Cognitive deficits antedate the clinical onset of the illness, may worsen over time, and are more strongly correlated with functional outcome then severity of positive symptoms (Green, 1996; Harvey et al., 1998; Marder & Fenton, 2004). In addition, patients with schizophrenia frequently exhibit affective symptoms during both the psychotic phase and the residual phase of the illness.

The course of schizophrenia is typically characterized by long-term social and occupational impairment punctuated by periods of decompensation during which psychotic symptoms worsen or reappear. Thus, treatment strategies need to target the acute psychotic phase of the disorder, achieve maintenance of symptom improvement or remission, and reduce relapse risk in long-term treatment. The illness course and outcome are variable among individuals, although complete symptom remission and return to premorbid function is not common. Progressive deterioration over time characterizes the course of illness for most patients, particularly in the first few years of the illness. The first antipsychotic drug, chlorpromazine, was introduced in 1954 and was followed by several similar drugs, including fluphenazine, haloperidol, loxapine, perphenazine, thiothixene, thioridazine, and trifluoperazine. With the later introduction of clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, and lurasidone, antipsychotic drugs have come to be classified as typical (chlorpromazine-like) or first-generation antipsychotics (FGAs) versus atypical or (clozapine-like) second-generation antipsychotics (SGAs). SGAs were initially thought to produce fewer extrapyramidal side effects (EPS) and cases of tardive dyskinesia than conventional drugs, to have greater efficacy in refractory patients and against negative symptoms, and to induce only limited prolactin elevation, although in recent years it has become clear that these differences are not as pronounced as initially thought and may not be clinically meaningful. Both FGAs and SGAs have been clearly demonstrated to be effective and safe for the acute and maintenance phases of treatment for schizophrenia. Notably, a landmark study by Kane, Honigfeld, Singer, and Meltzer (1988), which compared clozapine to chlorpromazine, demonstrated superior efficacy of clozapine in reducing symptoms in 30% of rigorously defined treatment-resistant patients, and the superiority of clozapine to other antipsychotics has been confirmed in a number of studies. Numerous studies have demonstrated that continuation of antipsychotic medication beyond treatment of the acute episode is necessary to reduce the risk of psychotic relapse, as evidenced by the fact that most patients will experience a clinical worsening if their treatment is discontinued (Carpenter et al., 1990; Davis, 1975; Gaebel et al., 1993; Herz et al., 1991; Hogarty, Ulrich, Mussare, & Aristigueta, 1976; Hogarty et al., 1988; Johnson, Ludlow, Street, & Taylor, 1987; Jolley, Hirsch, Morrison, McRink, & Wilson, 1990; Kane & Lieberman, 1987; Kane, Rifkin, Quitkin, Nayak, & Ramos-Lorenzi, 1982; Kane et al., 1983, 1993; Kane, Woerner, & Sarantakos, 1986; Marder et al., 1987; Robinson et al., 1999a; Schooler, Keith, Severe, & Mathews, 1993; Schooler et al., 1993). Concomitant medications such as benzodiazepines, lithium, carbamazepine, valproic acid, dopamine agonists, and glutamatergic agonists have been used alone and in combination with antipsychotic drugs to improve treatment response, although clear demonstration of the effectiveness of these strategies is lacking. In addition, antidepressants have been used extensively to treat depressive symptoms associated with schizophrenia. We will begin with a review of the controlled trial literature for FGAs and SGAs, followed by a review of the various augmentation strategies that have been evaluated.

FIRST-GENERATION ANTIPSYCHOTICS

The introduction of the prototypical conventional antipsychotic drug chlorpromazine in the 1950s, with the subsequent development of other antipsychotic agents with similar pharmacological activity, led to a revolution in the treatment of schizophrenia. These

drugs are credited with providing the first effective medical management strategy for schizophrenia and constitute one of the great medical advances of the 20th century. Early doubts regarding the efficacy of these compounds led to the design of rigorous clinical trials, such as the placebo-controlled, double-blind study with thoughtful subject inclusion and exclusion criteria, random treatment assignment, and the use of standardized rating instruments to prove the value of these drugs. More than 100 placebo-controlled trials have conclusively demonstrated the effectiveness of antipsychotic drugs (Davis, Barter, & Kane, 1989). A representative sample of methodologically rigorous acute treatment trials that demonstrate the efficacy of FGAs commonly used and currently available in the United States, compared with placebo, is given in Table 6.1. Placebo-controlled studies in which antipsychotic efficacy could not be demonstrated are generally restricted to poorly designed studies that involved doses of chlorpromazine less than 300 mg/day (Klein & Davis, 1969). Of the FGAs, haloperidol (Joy, Adams & Lawrie, 2006) and chlorpromazine (Adams et al., 2005) are the best characterized in terms of modern double-blind, randomized controlled trials (RCTs), although when FGAs have been compared to SGAs in high-quality studies there have not been clear differences in efficacy. Two of them, haloperidol and fluphenazine, are available in depot form. Despite improvement in psychotic symptoms, which is clinically important and was partly responsible for deinstitutionalization, patient functioning and social reintegration did not consistently improve with the use of FGAs. This disappointing observation was made soon after the introduction of these drugs into clinical practice (Schooler, Goldberg, Boothe, & Cole, 1967). Although a large number of antipsychotics have become available to clinicians in the United States since 1954, an extensive body of evidence has confirmed that most of these drugs, with a few notable exceptions, are essentially similar in their efficacy profiles, although an individual patient may show a better response to one particular drug than to another (Gardos, 1974). Table 6.2 lists the efficacy demonstrated in controlled clinical trials of a representative sample of antipsychotic drugs compared to the reference drugs chlorpromazine and haloperidol.

Accumulating data suggest that the time to onset of therapeutic effect of antipsychotic drugs during the treatment of an acute episode of schizophrenia may be quite variable. Davis and colleagues (1989) reported that onset of effect is usually manifest within the first 1 to 3 weeks and that most gains are noted within 6 to 8 weeks. Agid, Kapur, Arenovich, and Zipursky (2003) conducted a meta-analysis of 42 double-blind comparator-controlled studies and found that antipsychotic effect was evident within the first week of treatment and that improvement in the first 2 weeks was greater than during any subsequent 2-week period. In a double-blind, placebo-controlled study comparing intramuscular olanzapine with intramuscular haloperidol, Kapur and colleagues (2005) reported that onset of specific antipsychotic effect was evident within the first 24 hours, and that improvement in psychosis was independent of change in agitation and excitement. However, some patients, including first-episode patients (Lieberman, 1993; Robinson et al., 1999b), may require several months to achieve their full clinical response and symptom remission. In another study of patients with first-episode schizophrenia, Emsley, Rabinowitz, and Medori (2006) found that clinical response (greater than 20% improvement in total Positive and Negative Symptom Scale [PANSS] score) was achieved in 77% of the sample, although the time to response varied from 1 to greater than 8 weeks.

When a patient fails to respond to a standard course of treatment, clinicians generally employed maneuvers such as increasing the dose, switching to another typical antipsychotic, or maintaining the initial treatment for an extended trial. However, little early evidence from controlled clinical trials supports the efficacy of any of these strategies (Kinon et al., 1993; Levinson et al., 1990; Rifkin, Doddi, Karajgi, Borenstein, & Wachspress, 1991; Van Putten, Marder, & Mintz, 1990; Volavka et al., 1992). More recently it was shown in the large Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study that switching to a new medication yielded no advantage over staying on the previous medication (Rosenheck et al., 2009), and in another trial switching from olanzapine, quetiapine, or risperidone to aripiprazole led to reduction in weight and triglycerides but at the expense of higher discontinuation rates at 24 weeks (43.9% vs 24.5%) (Stroup et al., 2011). Similarly, switching from haloperidol decanoate or fluphenazine decanoate to risperidone long-acting injectable led to higher rates of discontinuation and no differences in psychopathology (Covell et al., 2012). Switching from antipsychotic polypharmacy to monotherapy also led to increased rates of discontinuation

TABLE 6.1 Representative Studies of Definitive Antipsychotic Drug Efficacy in Acute Schizophrenia/Schizoaffective Psychotic Exacerbation (vs. Placebo or Active Placebo)

Drug	*Number of Studies*	*Reference*
FGAs		
Chlorpromazine	8	Clark et al. (1968) Hollister et al. (1960) Casey et al. (1960a, 1960b) Kurland et al. (1961) NIMH-PSC (1964) Casey et al. (1960) Schiele et al. (1961) Adelson & Epstein (1962)
Fluphenzine	2	NIMH-PSC (1964)
Haloperidol	9	Vestre et al. (1962) Garry & Leonard (1962) Azima et al. (1960) Samuels et al. (1961) Chouinard et al. (1993) Brandrup & Kristjansen (1961) Beasley et al. (1996b) Marder & Meibach (1994) Okasha & Twefik (1964) Reese & Davies (1965)
Loxapine	3	Simpson (1976) Van der Velde & Kiltie (1975) Clark et al. (1972)
Perphenazine	3	Kurland et al. (1961) Adelson & Epstein (1962)
Trifluoperazine	3	Casey et al. (1960a, 1960b) Hollister et al. (1960) Adelson & Epstein (1962)
Thiothixene	4	Wolpert et al. (1968) Huang et al. (1987) Yilmaz (1971) Gallant et al. (1966)
Thioridazine	2	NIMH-PSC (1964) Schiele et al. (1961)
SGAs		
Clozapine	2	Shopsin et al. (1979) Pickar et al. (1992)
Risperidone	2	Marder & Meibach (1994) Chouinard et al. (1993)
Olanzapine	2	Beasley et al. (1996a) Beasley et al (1996b)
Quetiapine	2	Borison et al. (1996) Small et al. (1997)
Ziprasidone	2	Keck et al. (1998) Daniel et al. (1999)

TABLE 6.1 (continued)

Drug	*Number of Studies*	*Reference*
Aripiprazole	3	Kane et al. (2002) Potkin et al. (2003) McEvoy et al. (2007a)
Paliperidone	6	Kane et al. (2007) Davidson et al. (2007) Canuso et al. (2009) Marder et al. (2007) Shah & Joshi (2011) Canuso et al. (2010)
Lurasidone	4	Nakamura et al. (2009) Meltzer et al. (2011) Ogasa et al. (2013) Nasrallah et al. (2013)
Iloperidone	4	Potkin et al. (2008) Cutler et al. (2008)
Asenapine	2	Potkin et al. (2007) Kane et al. (2010a)

at 6 months—86% among those staying on polypharmacy were still taking both medications compared to 69% taking the same medication among those switching to monotherapy—although symptom control was no different between the two groups. Nonetheless, two thirds of patients who switched were successful, and monotherapy resulted in weight loss (Essock et al., 2011), suggesting that discontinuing polypharmacy is a reasonable course of action in many instances, particularly if there is a compelling reason. This is consistent with an earlier meta-analysis that found that antipsychotic polypharmacy was associated with less study-specific inefficacy and all-cause discontinuation than switch to monotherapy (Correll, Rummel-Kluge, Corves, Kane, & Leucht, 2009).

Significant efforts are under way to identify factors that may be associated with antipsychotic treatment response and refractoriness. For example, a delay in the initiation of antipsychotic drug treatment following onset of psychosis in first-episode schizophrenia (Loebel et al., 1992), and in the treatment of acute exacerbations (May et al., 1976; Wyatt, 1995), may be associated with poorer clinical outcomes. Robinson and colleagues (1999b) reported that 87% of their sample of first-episode patients with schizophrenia or schizoaffective disorder responded to treatment within 1 year, with a median response time of 9 months. They demonstrated that male gender, a history of obstetric complications, poorer attention at baseline, more severe hallucinations and delusions, and the development of EPS during antipsychotic treatment were associated with a significantly lower likelihood of response.

Numerous studies have demonstrated that continuation of antipsychotic medication beyond treatment of the acute episode is necessary to reduce the risk of psychotic relapse, as evidenced by the fact that most patients will experience a clinical worsening if their treatment is discontinued (Davis, 1975; Kane & Lieberman, 1987). Controlled clinical trials of drug discontinuation demonstrate that after 1 year of maintenance treatment, 30% of patients will relapse on medication compared with a rate of 65% in patients who have undergone placebo substitution. Even those patients who have been successfully maintained in the community for 2 to 3 years on antipsychotic drugs will demonstrate a relapse rate of 66% by 1 year after their treatment is discontinued (Hogarty, Ulrich, Mussare, & Aristigueta, 1976). First-episode patients show a slightly lower relapse rate, with 40% of patients on placebo experiencing a relapse, compared with none while on medication during the year following initial recovery (Kane, Rifkin, Quitkin, Nayak, & Ramos-Lorenzi, 1982). Robinson and colleagues (1999a) showed that discontinuing drug therapy increased the risk of

TABLE 6.2 Representative Studies of Relative Antipsychotic Drug Efficacy in Acute Schizophrenia/Schizoaffective Exacerbation (vs. Chlorpromazine [CPZ] and/or Haloperidol [HAL])

	Number of Studies				
Drug	*Superior to CPZ*	*Equal to CPZ*	*Superior to HAL*	*Equal to HAL*	*Reference*
FGAs					
Fluphenazine		3			Cole et al. (1964) NIMH-PSC (1964) Laskey et al. (1962) Hanlon et al. (1965)
Haloperidol	2	1			Pratt et al. (1964) Fox et al. (1964) 1 Serafetinides et al. (1972)
Loxapine	1	1		2	Tuason et al. (1984) Rifkin et al. (1984) Fruensgaard et al. (1977) Tuason (1986)
Perphenazine		4			Adelson & Epstein (1962) Hanlon et al. (1965) Kurland et al. (1961) Casey et al. (1960)
Trifluoperazine		4			Adelson & Epstein (1962) Schiele et al. (1961) Hanlon et al. (1965) Hollister et al. (1960)
Thiothixene		1			Rickels et al. (1978)
Thioridazine		3			Schiele et al. (1961) Cole et al. (1964) NIMH-PSC (1964) Laskey et al. (1962)
SGAs					
Clozapine	4	1		1	Gelenberg & Doller (1979) Leon (1979) Shopsin et al. (1979) Kane et al. (1988) Claghorn et al. (1987) Klieser et al. (1994)
Risperidone			4	5	Peuskens (1995) Ceskova & Svestka (1993) Min et al. (1993) Borison et al. (1992) Moller et al. (2008) Chouinard et al. (1993) Marder & Meibach (1994) Claus et al. (1992) Muller-Spahn (1992)
Olanzapine	1		2	1	Beasley et al. (1996b) Tollefson et al. (1997) Beasley et al. (1997a) Dossenbach et al. (2007)

TABLE 6.2 (continued)

	Number of Studies				
Drug	*Superior to CPZ*	*Equal to CPZ*	*Superior to HAL*	*Equal to HAL*	*Reference*
Quetiapine		1		2	Peuskens & Link (1997) Arvanitis et al. (1997) Copolov et al. (2000)
Ziprasidone				1	Goff et al. (1998)
Aripiprazole				2	Kasper et al. (2003)

relapse almost five times in a sample of patients with first-episode schizophrenia and schizoaffective disorder. This study also showed an 82% cumulative risk of relapse for patients who had recovered from a first episode of psychosis but were not continued on antipsychotic medication. Those who had one relapse within 5 years had a 78% chance of having a second relapse and an 86% chance of having a third. Thus, maintenance antipsychotic therapy seems justified, even for patients recovering from their first episode of schizophrenia. The benefits of maintenance antipsychotic drug treatment, however, are tempered by the inherent risk to the patient of long-term side effects such as the development of tardive dyskinesia and health sequelae of weight gain and dyslipidemia secondary to metabolic abnormalities caused by antipsychotics. Limiting antipsychotic drug exposure by introducing "drug holidays" or reducing the dose has intuitive appeal for minimizing side-effect risk. However, maintenance studies of the dose-response relationship for up to 1 year of continuous antipsychotic drug treatment indicate that standard drug doses (fluphenazine decanoate 12.5 to 50 mg biweekly; haloperidol decanoate 50 to 200 mg monthly) provide significantly greater prophylaxis against relapse than do doses of one half to one tenth as much (Hogarty et al., 1988; Johnson, Ludlow, Street, & Taylor, 1987; Kane et al., 1983; Kane, Woerner, & Sarantakos, 1986; Kane et al., 1993; Marder et al., 1987; Schooler, Keith, Severe, & Mathews, 1993), although the lower doses may be associated with better social adjustment and fewer EPS. A targeted approach that involves slowly titrating patients off maintenance medication with reintroduction of the medication rapidly during presumptive incipient relapsing has not been found to be more effective than the continuous administration of maintenance medication and is associated with risks of symptom exacerbation and relapse (Carpenter et al., 1990; Gaebel et al., 1993; Herz et al., 1991; Jolley, Hirsch, Morrison, McRink, & Wilson, 1990; Schooler et al., 1993).

SECOND-GENERATION ANTIPSYCHOTICS

SGAs initially offered hope for enhanced efficacy in the treatment of schizophrenic psychopathology with a reduced burden of extrapyramidal motor dysfunction. The number of double-blind studies comparing the acute treatment effects of atypical antipsychotics with the effects of their typical counterparts and the number of studies comparing effects in treatment-refractory populations have continued to grow rapidly. We will review the available evidence supporting the use of each drug in acute, chronic, and treatment-resistant schizophrenia. This is followed by summaries of the meta-analyses of published studies, the CATIE, and side-effect profiles of the SGAs.

Clozapine

Two reviews summarizing a total of 45 studies compared clozapine to FGAs in the treatment of non–treatment-resistant patients and hinted at the superiority of clozapine with respect to the proportion of patients responding to clozapine, the amount of their response, and a small albeit statistically nonsignificant advantage in long-term relapse rate (Baldessarini & Frankenburg, 1991; Wahlbeck, Cheine, & Essali, 2000). When studies that included only patients with treatment-resistant schizophrenia are selected, the superiority of clozapine over typical antipsychotics is most consistently demonstrated.

A pivotal study (Kane et al., 1988) of the effectiveness of clozapine in treatment-resistant schizophrenia entered 268 such patients into a double-blind comparison with chlorpromazine. Treatment resistance was defined as having failed to respond to at least three prior antipsychotics and without any period of good functioning in the past 5 years, and then not responding to a single-blind 6-week haloperidol prospective lead-in trial. At 6 weeks, 30% of the clozapine-treated group but only 4% of the chlorpromazine-treated group met the a priori response criteria of a reduction greater than 20% from baseline in the Brief Psychiatric Rating Scale (BPRS) total score plus either a posttreatment Clinical Global Impression (CGI) score of 3 (mild) or lower or a posttreatment BPRS total score of 35 or lower. Since the initial study by Kane and colleagues, several double-blind comparisons of clozapine and an FGA have been conducted in patients with treatment-resistant schizophrenia (Buchanan, Breier, Kirkpatrick, Ball, & Carpenter, 1998; Hong, Chen, Chiu, & Sim, 1997; Kane et al., 2001; Kumra et al., 1996; Rosenheck et al., 1997), as well as an open-label study with random treatment assignment and long-term follow-up (Essock, Hargreaves, Covell, & Goethe, 1996), and all have been consistent with the notion that clozapine displays superior efficacy in treatment-resistant schizophrenia. A meta-analysis of seven trials comparing clozapine to typical antipsychotic drugs in treatment-refractory schizophrenia (Chakos, Lieberman, Hoffman, Bradford, & Sheitman, 2001) showed an advantage for clozapine with regard to total psychopathology, categorical response to treatment (measure of the number of patients who met an arbitrary cutoff for response), EPS, tardive dyskinesia, and study completion rates. Finally, the efficacy of clozapine in the maintenance phase of treatment is supported by three open-label studies (Breier, Buchanan, Irish, & Carpenter, 1993; Meltzer, Burnett, Bastani, & Ramirez, 1990; Miller, Perry, Cadoret, & Andreasen, 1992) that suggest clozapine reduces rehospitalization rates.

Almost certainly because they are a preselected group of the most treatment-refractory individuals, a considerable proportion of patients treated with clozapine do not respond or respond only partially to clozapine and are left with substantial residual psychopathology. A review of data from clozapine clinical trials by Buckley, Wiggins, Sebastian, and Singer (2001) found that about half of patients with treatment-refractory symptoms do not respond to clozapine. An augmentation strategy for patients who have failed to respond to an adequate clozapine trial that has been evaluated in several controlled and open trials is the use of an antipsychotic with high D_2 antagonist affinity to supplement the low D_2 occupancy of clozapine. Three double-blind, placebo-controlled, randomized studies of augmentation of clozapine with risperidone have been published, with one suggesting benefit of risperidone augmentation of clozapine (Josiassen et al., 2005) and two finding no benefit (Honer et al., 2006; Yagcioglu et al., 2005). In summary, the controlled studies in aggregate do not lend support to augmentation of clozapine with other antipsychotics in patients who either have failed to respond or have had a suboptimal response to an adequate trial of clozapine alone.

Clozapine remains the only antipsychotic specifically approved by the U.S. Food & Drug Administration (FDA) for treatment-resistant schizophrenia. Clozapine is also approved for reduction of suicide risk in patients with schizophrenia. The controlled trial that led to this indication (Meltzer et al., 2003) included 980 patients who were at relatively high risk of suicide and were randomized to double-blind treatment with either clozapine or olanzapine and followed for up to 2 years; approximately 25% of the sample had treatment-resistant schizophrenia. Suicidal behavior was significantly less in patients treated with clozapine versus olanzapine, as reflected by fewer clozapine-treated patients attempting suicide, requiring hospitalization or rescue interventions to prevent suicide, or requiring concomitant treatment with antidepressants or anxiolytics.

Unfortunately, the reported incidence rate of 1% for clozapine-induced agranulocytosis (Alvir, Lieberman, Safferman, Schwimmer, & Schaaf, 1993) has limited the extent of the drug's use in clinical practice, although with appropriate monitoring of the granulocyte count (weekly for the first 6 months, every other week for the second 6 months, and every 4 weeks thereafter) the risk of morbidity and mortality from agranulocytosis is almost entirely eliminated. Clozapine has also been associated with an increased risk of myocarditis and a dose-dependent risk for seizures; other side effects that commonly occur include sedation, weight gain, hypotension, tachycardia, hypersalivation, and constipation. In summary, the demonstrated efficacy of clozapine among the subgroup of refractory patients, with no acute EPS and the absence of risk for tardive dyskinesia, represents a

landmark achievement in psychopharmacology. The success of clozapine provided the impetus for an enormous research effort that has resulted in the development of several other atypical antipsychotic drugs.

Risperidone

A number of double-blind RCTs have been published that compared the efficacy of risperidone to placebo and/or FGA or SGA in the treatment of acute schizophrenic exacerbations. In these studies, risperidone has been consistently superior to placebo. Some studies have shown the superiority of risperidone compared to haloperidol with respect to clinical efficacy (Chouinard et al., 1993; Marder & Meibach, 1994), while others have shown that the efficacies of risperidone and haloperidol are indistinguishable (Moller et al., 2008; Peuskens, 1995), including in first-episode patients (Schooler et al., 2005). Studies have been more consistent in showing that risperidone is superior to haloperidol with respect to EPS, although the difference may not be as pronounced at higher doses of risperidone (Chouinard et al., 1993; Marder & Meibach, 1994; Moller et al., 2008; Peuskens, 1995; Schooler et al., 2005). One smaller RCT with a total of 78 patients split across four treatment groups suggested that risperidone was superior to quetiapine and equivalent to olanzapine with respect to the percentage of patients discontinuing after 8 weeks (Hatta et al., 2009), and another larger RCT showed that risperidone and ziprasidone were equivalent with respect to efficacy but not side effects, with ziprasidone being superior in terms of EPS, prolactin elevation, and weight gain (Addington et al., 2009). Risperidone appears to be superior to haloperidol with respect to EPS liability, but it causes more prolactin elevation, more early weight gain, and similar weight gain at later endpoints (Schooler et al., 2005). It should be noted that addition of aripiprazole to risperidone (or quetiapine) in one RCT with a total of 323 patients did not demonstrate any improvement in psychiatric symptoms compared to risperidone alone (Kane et al., 2009). Furthermore, a rater-blinded, randomized controlled 4-week trial suggested that lack of response with risperidone at 2 weeks predicted lack of response at 4 weeks, a relationship that did not hold for olanzapine (Hatta et al., 2011).

Hunter, Joy, Kennedy, Gilbody, and Song (2003) conducted a review of all RCTs comparing risperidone to any FGA treatment for individuals with schizophrenia or other similar serious mental illnesses. In the short term, risperidone was more likely to produce an improvement in the PANSS compared with haloperidol (n = 2,368, nine RCTs). A similar, favorable outcome for risperidone was found in long-term studies (n = 859, two RCTs). Risperidone was also more likely to reduce relapse at 1-year follow-up compared with haloperidol (n = 367, one RCT). Fewer participants treated with risperidone left studies before completion, in both short-term (n = 3,066, 16 RCTs) and long-term trials (n = 1,270, four RCTs). Patients given risperidone had significantly fewer general movement disorders (including EPS) than those receiving FGAs (n = 2,702, 10 RCTs). Significantly fewer participants given risperidone used antiparkinsonian drugs (n = 2,524, 11 RCTs). Four studies (n = 1,708) found risperidone-treated patients were more likely to gain weight than were patients treated with FGAs. Risperidone was no more or less likely than haloperidol to cause sexual problems such as erectile dysfunction (n = 106, two RCTs).

The efficacy of risperidone compared with haloperidol in longer-term treatment has also been rigorously evaluated in RCTs. Some early trials suggested that risperidone might be superior to FGAs (usually haloperidol) with respect to relapse risk (Csernansky, Mahmoud, & Brenner, 2002). A naturalistic follow-up study showed that time to readmission to an inpatient psychiatric unit after 2 years was longer in risperidone and olanzapine-treated patients compared to those being treated with FGAs (Rabinowitz et al., 2001). Another RCT (Schooler et al., 2005) of risperidone and haloperidol in first-episode patients found that relapse rates were significantly lower in risperidone-treated patients (42% and 55%, respectively) over a median follow-up period of 206 days, and median time to relapse was longer in risperidone-treated patients (466 days for risperidone-treated patients vs. 205 days for haloperidol-treated patients). The advantage for risperidone in reducing relapse risk was evident even though both groups had comparable symptom improvement. On the other hand, in the CATIE study, patients who were switched from perphenazine to risperidone due to lack of efficacy had significantly shorter time to discontinuation (3.6 months) compared to switching to quetiapine (9.9 months) or olanzapine (7.1 months), possibly due to similarities in potency and side-effect profile between perphenazine and risperidone (Stroup et al., 2007). A large

RCT with a total of 404 patients demonstrated that continuing risperidone at the dose that was effective during acute exacerbation was superior to 50% dose reduction at 4 or 26 weeks (30.5% vs 19.5% vs 9.4%, respectively) (Wang et al., 2010). The efficacy of risperidone compared with conventional antipsychotics in treatment-refractory populations has also been studied, although to a lesser degree. Multiple rigorous RCTs have not been able to clearly demonstrate any utility of risperidone in treatment-refractory patients (Azorin et al., 2001; Volavka et al., 2002; Wirshing et al., 1999), although RCTs comparing risperidone with clozapine using less strict criteria for the definition of treatment-resistant schizophrenia (Bondolfi et al., 1998; Klieser et al., 1995) had somewhat more optimistic results for risperidone.

Risperidone has recently become available in a long-acting injectable formulation for intramuscular administration every 2 weeks. The efficacy and safety of long-acting risperidone have been evaluated in two large clinical trials (Fleischhacker et al., 2003; Kane et al., 2003). Kane and colleagues (2003), in a 12-week, randomized, double-blind, placebo-controlled, multicenter trial, treated 400 patients with schizophrenia with either long-acting risperidone (25 mg, 50 mg, or 75 mg every two weeks) or placebo injection; they found that long-acting risperidone was significantly more effective than placebo in terms of mean total PANSS, as well as mean positive and mean negative subscale scores. The 75-mg dose was associated with no efficacy advantage over the lower doses and was associated with an increased rate of adverse events; it is therefore not a marketed dose. Another small RCT suggested that risperidone long-acting injectable (LAI) (n = 26) was superior to oral risperidone in terms of adherence (89% vs 59%) (Weiden et al., 2009). A randomized, active-controlled, 2-year trial with 666 patients with schizophrenia suggested that risperidone LAI was superior to quetiapine in terms of relapse at 2 years (16.5% vs 31.3%) (Gaebel et al., 2010). A nationwide cohort study in Finnish schizophrenia patients (N = 2,588 total) found that the risk of relapse with risperidone LAI (and other depots) was one third of that for the equivalent oral formulation (Tiihonen et al., 2011). Similarly, a prospective observational schizophrenia study with 1,345 risperidone LAI-treated patients showed that risperidone LAI was superior to oral antipsychotics in treatment retention and CGI as well as reduction in number and days of hospitalizations (Olivares et al., 2009). However, a recent rigorous RCT with 369 total patients compared risperidone LAI to psychiatrist antipsychotic of choice and found no difference in hospitalization rate or efficacy, although risperidone LAI was inferior with respect to EPS (Rosenheck et al., 2011). Another smaller 6-month RCT followed by 6 months of naturalistic follow-up compared patients continued on haloperidol decanoate or fluphenazine decanoate to individuals switching to risperidone LAI and found a higher discontinuation rate in switchers, no differences in psychopathology, and more weight gain (Covell et al., 2012).

In summary, the available data suggest that risperidone may be somewhat more effective than typical antipsychotics in acute and maintenance treatment; however, its utility in treatment-refractory populations has not been convincingly established, although there is some evidence it may be superior to conventional antipsychotics but not as effective as clozapine in this population. Persistent prolactin elevation remains a problem with risperidone. The advantage of lower EPS liability compared with typical antipsychotics is diminished at higher doses (more than 6 mg/day), although higher doses are usually not necessary for therapeutic effect.

Olanzapine

The FDA approved olanzapine in 1996 for the treatment of schizophrenia. Since that time, many RCTs and large prospective studies have accumulated. At least one large RCT has demonstrated the superiority of olanzapine (Beasley et al., 1996) and olanzapine LAI (Lauriello et al., 2008) compared to placebo in the treatment of acute schizophrenia, and multiple large RCTs in acute schizophrenia have demonstrated either that olanzapine and haloperidol are similar in efficacy (Beasley et al., 1996) or that olanzapine may be superior to haloperidol with respect to improvement in positive and negative symptoms, although in some studies only at higher doses (Beasley et al., 1997; Tollefson et al., 1997). Olanzapine has similarly been shown to be superior to chlorpromazine with respect to efficacy in a recent RCT (Dossenbach et al., 2007). Olanzapine's side-effect profile also differed from haloperidol in that it had lower EPS liability and caused less prolactin elevation (Beasley et al., 1996, 1997; Tollefson et al., 1997) but more early weight gain (Tollefson et al., 1997). The aforementioned findings

are consistent with the findings of a meta-analysis that found that olanzapine was superior to typical antipsychotics (14 RCTs, $N = 3,344$) in terms of total PANSS as well as positive and negative symptom scores, and caused fewer EPS but significantly more weight gain. Olanzapine did not differentiate from other SGAs on efficacy outcomes, although it was associated with fewer EPS but caused greater weight gain (11 RCTs, $N = 1,847$). A number of more recent RCTs have also been unable to demonstrate superiority of olanzapine relative to other SGAs. In an 8-week RCT in acute schizophrenia with 75 total patients, there were no significant differences between quetiapine, risperidone, and olanzapine on PANSS total score (Sacchetti, Valsecchi, & Parrinello, 2008). Another RCT with 116 total patients showed no efficacy difference between olanzapine, risperidone, or molindone in the treatment of acute schizophrenia (Sikich et al., 2008). In contrast to most studies demonstrating no efficacy difference between olanzapine and other SGAs, one 6-week acute RCT with 703 patients suggested that olanzapine was superior to aripiprazole in terms of efficacy measures and time to discontinuation (Fleischhacker et al., 2009). Interestingly, a large ($N = 599$ patients) RCT using multiple doses of olanzapine (10, 20, and 40 mg) demonstrated no difference on the PANSS total but a dose-response effect with respect to prolactin elevation and weight gain, suggesting that 10 mg is a reasonable initial dose for non–treatment-resistant patients (Kinon et al., 2008). One post hoc reanalysis of a large multicenter double-blind RCT ($N = 1,996$) suggested that patients who showed little to no reduction in symptoms 2 weeks after starting olanzapine were unlikely to show a response of any kind at 4 to 6 weeks (Leucht, Shamsi, Busch, Kissling, & Kane, 2008), although the opposite was shown in another RCT (Hatta et al., 2011). It should also be noted that olanzapine oral tablets have been shown in a 13-week, randomized, open-label trial with 377 schizophrenic and schizoaffective patients to be equivalent in efficacy to risperidone LAI (Keks, Ingham, Khan & Karcher, 2007). In a 24-week RCT with over 1,000 patients, olanzapine LAI and oral olanzapine were noted to be equivalent with respect to exacerbation likelihood and efficacy (Kane et al., 2010).

The potential of olanzapine in maintaining long-term therapeutic effect in comparison with both FGAs and SGAs has also been studied extensively. Consistent with acute treatment studies, a recent 52-week RCT with 400 total patients split among olanzapine, quetiapine, and risperidone treatment groups showed that these medications appeared comparable with respect to effectiveness, although olanzapine held a small advantage with respect to positive symptoms at 12 and 52 weeks (McEvoy et al., 2007). However, a number of long-term studies comparing olanzapine to other antipsychotics have detected differences in clinical effectiveness (Tran, Dellva, Tollefson, Wentley, & Beasley, 1998). The data from the extension phases of three double-blind studies comparing olanzapine with haloperidol were pooled to form one group for each drug. Olanzapine-treated subjects experienced fewer relapses than haloperidol-treated subjects, and the Kaplan-Meier estimated 1-year risk of relapse was 19.7% with olanzapine and 28% with haloperidol. Similar advantages for olanzapine were evident in a study in patients with first-episode schizophrenia. Lieberman and colleagues (2003) conducted a double-blind, randomized study of olanzapine and haloperidol in first-episode patients and found that in treatment of the acute phase of the illness, both drugs were comparable in efficacy. However, at the last observation point (12 weeks), significantly more patients were still in treatment in the olanzapine arm versus the haloperidol arm (67% vs. 54%). Evidence for reduced discontinuation rates with olanzapine in comparison to FGAs has accumulated in both RCTs and prospective observational studies. As will be discussed in greater detail later, this was noted in the large CATIE trial, in which olanzapine had the longest time to discontinuation in comparison to perphenazine, risperidone, quetiapine, and ziprasidone (Lieberman et al., 2005). In a 3-year prospective, observational study with 7,728 patients, medication discontinuation rates were lowest with olanzapine (36.4%) and clozapine (33.8%) and higher for conventional oral FGAs (53.1%) and depot FGAs (50.2%) (Haro et al., 2007). Similarly, in an RCT with a total of 498 first-episode patients, discontinuation for any cause within 12 months was 72% for haloperidol, 40% for amisulpride, 33% for olanzapine, 53% for quetiapine, and 45% for ziprasidone (all significantly lower than haloperidol, despite indistinguishable efficacy) (Kahn et al., 2008). Another large observational study, the Schizophrenia Health Outcomes Observational (SOHO) study, with 1,688 patients, noted similar findings, namely that medication

maintenance at 3 years was highest with clozapine (57.6%) and olanzapine (48.3%) and lowest with quetiapine (19%). Treatment discontinuation was less frequent with olanzapine than with risperidone, depot FGA, oral FGA, or quetiapine, and similar to clozapine; and longer maintenance was associated with higher social abilities and better cognitive status (Ciudad et al., 2008). Findings were similar in the SOHO study in previously untreated patients initiating monotherapy (Haro, Novick, Suarez, & Roca, 2009) and another large observational study with 7,658 patients (Dossenbach et al., 2008). An exception to the trend of decreased rates of discontinuation in patients taking olanzapine may be in patients who have a substance use disorder, for whom all drugs appeared similar in terms of rates of discontinuation in the CATIE study ($N = 371$) (Swartz et al., 2008). Although most studies have not shown long-term differences in efficacy as measured by clinical scales, it was noted in the CATIE study that a higher proportion of olanzapine-treated patients maintained remission at 6 months (12.4%) in comparison to other antipsychotics (quetiapine, 8.2%; perphenazine, 6.8%; ziprasidone, 6.5%; and risperidone, 6.3%) (Levine, Rabinowitz, Ascher-Svanum, Faries, & Lawson, 2011).

The metabolic effects of olanzapine have also been studied and compared to a handful of other antipsychotics in mostly open-label or retrospective studies. In one study with 145 first-episode psychosis patients, metabolic changes were noted to be similar between haloperidol, olanzapine, and risperidone at 12 weeks (Perez-Iglesias et al., 2007), although using data from 246 patients in the CATIE study, it was found that olanzapine and quetiapine increased triglyceride levels, ziprasidone was neutral, and perphenazine and risperidone decreased triglycerides at 3 months (Meyer et al., 2008). In a retrospective chart review study with 296 patients, individuals started on SGAs had a three times higher incidence of metabolic syndrome than those started on FGAs, with the difference in incidence disappearing when olanzapine and clozapine patients were excluded from the analysis (De Hert et al., 2008). Finally, in another randomized, open-label prospective trial with 164 patients, it was noted that severity of weight gain increased from haloperidol to risperidone to olanzapine at 3 months, but there was no difference at 1 year (Perez-Iglesias et al., 2008).

A few studies have compared olanzapine with other antipsychotics in treatment-refractory patients with varying results. Conley and colleagues (1998), in a 6-week trial with 84 patients, described a study very similar in design to the original study by Kane and colleagues (1988) that established clozapine as a treatment for refractory schizophrenia. No differences were found between olanzapine and chlorpromazine for positive or negative symptoms or total psychopathology. Breier and Hamilton (1999), in a 6-week RCT of 526 patients who were determined to be partially responsive to FGAs, noted olanzapine to be superior to haloperidol in reducing positive and other symptoms in at least some patients. Volavka and colleagues (2002) also found olanzapine to be superior to haloperidol. A more recent small RCT ($N = 40$ patients total) also suggested that high-dose olanzapine was equivalent to clozapine with respect to efficacy at 6 weeks and 6 months (Meltzer et al., 2008), although another similarly sized RCT found that 66% of clozapine patients met response criteria whereas only 33% of olanzapine patients did, suggesting the superiority of clozapine (Kumra et al., 2008). On the whole, the available evidence suggests that olanzapine has some efficacy advantages over FGAs both in the acute and maintenance treatment phases of the illness and in the treatment of patients selected for prior treatment resistance to FGAs. However, substantial weight gain and metabolic disturbances have emerged as serious side effects.

Quetiapine

The FDA approved quetiapine in 1998, and its efficacy has been evaluated in several methodologically rigorous clinical trials. Two 6-week double-blind, placebo-controlled studies that enrolled 109 and 286 patients, respectively (Borison, Arvanitis, & Miller, 1996; Small, Hirsch, Arvanitis, Miller, & Link, 1997), and were composed of groups of patients with average treatment doses ranging from 209 mg to 407 mg, showed superiority of quetiapine to placebo in the treatment of psychotic symptoms. In a randomized, double-blind 6-week study (Peuskens & Link, 1997) that compared the efficacy of quetiapine to chlorpromazine among 201 patients, with doses up to 750 mg for each, no significant differences in efficacy were found.

Two 6-week RCTs in patients with schizophrenia have found quetiapine to be comparable to haloperidol with respect to efficacy but with fewer EPS (Arvantis & Miller, 1997; Copolov, Link, & Kowalcyk, 2000). Most of the studies comparing quetiapine to other SGAs, which include olanzapine and were described above, have suggested that quetiapine is comparable in efficacy to other SGAs (Sacchetti, Valsecchi, & Parrinello, 2008) although perhaps slightly inferior to olanzapine (McEvoy et al., 2007). On the other hand, quetiapine has demonstrated significantly inferior discontinuation rates to olanzapine, although not other SGAs, in the CATIE trial (Lieberman et al., 2005). Maintenance of remission at 6 months in the CATIE trial in quetiapine-treated patients was also inferior to olanzapine-treated patients (12.4% vs 8.2%) although similar to other SGAs and perphenazine (Levine, Rabinowitz, Ascher-Svanum, Faries, & Lawson, 2011). The findings in the SOHO study were even less favorable with respect to quetiapine, with medication maintenance at 3 years at 19% for quetiapine, which was the lowest of any medication examined in the study, including oral and depot typical antipsychotics, risperidone, olanzapine (48.3%), and clozapine (57.6%) (Ciudad et al., 2008). Finally, in an RCT of 498 first-episode patients, the 12-month discontinuation rate for quetiapine-treated patients was superior in comparison to haloperidol-treated patients, higher than for olanzapine-treated patients, and comparable to slightly higher than the rate for patients treated with other SGAs (Kahn et al., 2008).

The data for the effectiveness of quetiapine in treatment-resistant schizophrenia are very limited. Buckley, Goldstein, and Emsley (2004) reported a post hoc analysis of a double-blind randomized trial comparing quetiapine to haloperidol in 95 patients who had failed to improve with fluphenazine 20 mg/day in a 4-week, open-label phase. There was no clear advantage of quetiapine with respect to response rates based on the PANSS score (greater than 20% reduction) or CGI-improvement scale (CGI-I). Similarly, Conley and colleagues (2005) were not able to demonstrate a significant superiority of quetiapine or risperidone over fluphenazine in a small ($N = 38$) double-blind trial lasting 12 weeks in treatment-resistant patients. Overall, quetiapine appears to be similarly efficacious as conventional antipsychotics and is associated with minimal EPS and prolactin elevation. Sedation, orthostasis, and weight gain and other metabolic side effects may be problematic for some patients.

Ziprasidone

The FDA approved ziprasidone in February 2001 for the treatment of schizophrenia. Several studies have shown it to be effective against positive and negative symptoms of schizophrenia with little or no weight gain, a feature that distinguishes it from many of the current antipsychotics. Approval of ziprasidone was delayed by the FDA in 1998 pending more data on QT-interval changes in cardiac rhythm that theoretically could cause a dangerous arrhythmia called torsades de pointes. The drug was approved after the manufacturer submitted further safety data, including the fact that more than 4,000 patients had been treated in clinical trials with ziprasidone without evidence of torsades de pointes. This is supported by a more recent open-label study with 18,154 patients that showed no difference in non-suicide mortality between ziprasidone and olanzapine (Strom et al., 2011). The FDA does not require an electrocardiogram prior to treatment, and cardiac checkups during treatment are not mandated. To date, there has been no evidence from the clinical experience with ziprasidone that it is associated with cardiac toxicity.

The efficacy of ziprasidone in treating schizophrenia has been established in seven main studies: two versus placebo, one versus haloperidol, one versus risperidone, and three versus olanzapine. Keck and colleagues (1998) conducted a 4-week double-blind comparison of placebo and ziprasidone at 40 mg/day and 120 mg/day in 139 patients with schizophrenia and schizoaffective disorder, with ziprasidone at 120 mg/day producing statistically significant improvement in clinical symptomatology without causing movement disorders at a rate higher than placebo. Daniel and colleagues (1999) compared ziprasidone at 80 mg/day and 160 mg/day to placebo in a 6-week double-blind trial of 302 patients and demonstrated superiority of both doses to placebo in reducing clinical symptoms. Ziprasidone at 160 mg/day was also shown to significantly reduce depressive symptoms in patients with clinically significant depression at baseline. The drug was well tolerated and caused movement disorders and weight gain at rates similar to placebo.

In RCTs comparing ziprasidone to other antispychotics, ziprasidone has been shown to be equivalent in efficacy, often with a lower side-effect burden. Ziprasidone at doses of 160 mg/day has been shown to be equivalent in efficacy and superior with respect to EPS and prolactin elevation in comparison to haloperidol (Goff et al., 1998), indistinguishable from risperidone with respect to efficacy and side effects (Addington, Pantelis, Dineen, Benattia, & Romano, 2004), equivalent to olanzapine with respect to efficacy (Grootens et al., 2011; Simpson et al., 2005), and superior to olanzapine with respect to weight gain and lipid abnormalities (Meyer et al., 2008; Simpson et al., 2005). However, in a similar 28-week study, Breier and colleagues (2005) found that although both drugs were efficacious, olanzapine was superior to ziprasidone in the PANSS score (total and all subscales) as well as the CGI but inferior with respect to weight gain and lipid abnormalities.

The existing evidence on ziprasidone indicates that it is an effective antipsychotic, at least comparable to haloperidol in treating schizophrenia. It is associated with minimal weight gain and metabolic disturbances, is not sedating, and does not elevate serum prolactin. Further study and clinical experience are needed to determine whether this drug has a role in treatment-refractory schizophrenia or other special populations.

Aripiprazole

Aripiprazole was approved by the FDA in 2002 and has a mode of action that is distinct from those of currently available antipsychotic drugs. In addition to 5-HT_{2A} receptor antagonism, aripiprazole acts as a potent partial dopamine D_2 receptor agonist and a partial serotonin 5-HT_{1A} agonist. In Phase III comparative clinical studies, aripiprazole 15 to 30 mg/day was at least as effective as haloperidol and risperidone in short-term treatment of acute exacerbation of schizophrenia and superior to placebo. Consistent with the profile of most SGAs, aripiprazole has a low propensity to induce EPS. It is not associated with hyperprolactinemia and has a low liability for causing weight gain. Three short-term studies using Aripiprazole doses between 10 and 30 mg/day have established that aripiprazole is superior to placebo in terms of clinical improvement (Kane et al., 2002; Potkin et al., 2003; McEvoy, Daniel, Carson, McQuade, & Marcus, 2007).

A 26-week placebo-controlled trial in which aripiprazole 15 mg/day was administered to patients with stable chronic disease found that aripiprazole was significantly more effective than placebo in preventing relapse (34% vs. 57%), and there was no difference between treatments with respect to the overall incidence of adverse events (Pigott et al., 2003). The long-term efficacy and safety of aripiprazole (30 mg/day) relative to haloperidol (10 mg/day) was investigated in two 52-week, randomized, double-blind, multicenter studies with 1,294 patients with chronic schizophrenia who were in acute relapse (Kasper et al., 2003). Aripiprazole demonstrated long-term efficacy that was comparable or superior to that of haloperidol across all symptom measures, including significantly greater improvements for PANSS negative subscale scores and Montgomery-Asberg Depression Rating Scale (MADRS) total score. The time to discontinuation for any reason was significantly longer with aripiprazole than with haloperidol, and aripiprazole was associated with significantly lower scores than haloperidol on all EPS assessments. A 16-week RCT in 173 patients with schizophrenia or schizoaffective disorder showed that switching from olanzapine to aripiprazole led to significant weight loss, while continuation of olanzapine led to continued weight gain (Newcomer et al., 2008), although, as mentioned earlier, at the cost of higher discontinuation rates in switchers: 43.9% versus 24.5% (Stroup et al., 2011) or 16.8% versus 8.9% (Kane et al., 2009). Finally, aripiprazole has very recently become available in a depot formulation that has been shown to reduce the risk of impending relapse and to help patients maintain symptomatic clinical improvement in an RCT with 979 patients randomized to placebo maintenance or aripiprazole depot maintenance after an oral aripiprazole lead-in phase (Kane et al., 2009).

These data indicate that aripiprazole is effective in short- and long-term treatment of schizophrenia with efficacy that is at least comparable to that of other available antipsychotics. It also has a favorable side-effect profile that includes limited sedation, no prolactin elevation, and minimal weight gain. Aripiprazole has not been systematically evaluated in patients with treatment-resistant schizophrenia.

Paliperidone

Paliperidone, or 9-hydroxy-risperidone, a metabolite of risperidone, was approved by the FDA

for the treatment of schizophrenia in 2006 and schizoaffective disorder in 2009. It is available in oral and depot formulations, both of which have been studied in short- and long-term studies. In multiple 6 week, multicenter, double-blind RCTs, each with about 500 schizophrenia patients, paliperidone was superior to placebo in efficacy as measured by PANSS score and other clinical scales at multiple doses (3, 6, 9, 12, and 15 mg being the commonly studied doses) (Canuso et al., 2009; Davidson et al., 2007; Kane et al., 2007), including in patients who had previously received risperidone but were still acutely ill (Marder et al., 2007) and adolescents (Shah & Joshi, 2011). However, in at least one study lower-dose paliperidone (6 mg) was not superior to placebo in patients with schizoaffective disorder (Canuso et al., 2010). Paliperidone has also been compared in a few studies to other antipsychotics. In a 6 week RCT with 399 schizophrenia patients who received 2 weeks of monotherapy with paliperidone, quetiapine, or placebo, followed by the option to add another antipsychotic if needed for lack of efficacy, paliperidone was superior to quetiapine from days 5 through 14, and this superiority remained even if another antipsychotic was added (Canuso et al., 2009). In another RCT that allowed for periodic up-titrations due to lack of efficacy, the efficacy of paliperidone (maximum dose 12 mg) was comparable to olanzapine (maximum dose 20 mg) (Shah & Joshi, 2011). Furthermore, one RCT with 113 patients total suggested that the time to recurrence of a schizophrenia exacerbation was greater in paliperidone-treated patients compared to placebo (Kramer et al., 2007). Two studies have examined the side effects of paliperidone directly. In one study with 109 patients with schizophrenia or schizoaffective disorder, it was noted that the effect on QTc of daily doses of paliperidone extended-release 12 mg, the maximum recommended dose; paliperidone extended-release 18 mg; and quetiapine 800 mg were comparable (Hough et al., 2011). In a second RCT, paliperidone extended-release did not increase the ratio of triglycerides to high-density lipoproteins (TG/HDL ratio, a proxy measure for metabolic syndrome) or worsen insulin resistance, while olanzapine did both (Schreiner et al., 2012).

Paliperidone has also been studied extensively in the long-term treatment of schizophrenia, although mostly in open-label extension studies, typically 52 weeks in duration. In one open-label study with 215 paliperidone-treated patients, patients on paliperidone had fewer inpatient hospital days in the 52 weeks after starting the drug compared to the 52 weeks before, resulting in significant cost savings (Janicak, Wu & Mao, 2008). In another 52-week open-label study with 1,083 patients, many paliperidone-treated patients maintained their symptomatic improvements with few adverse events, with 47% of patients completing the open-label extension phase (Emsley et al., 2008), while in another flexibly dosed open-label extension study there was clinical improvement at 52 weeks in comparison to the start of the study (Kramer et al., 2010).

Paliperidone is also available in a depot formulation, paliperidone palmitate, which can be injected once a month. Paliperidone palmitate has been shown in at least three large placebo-controlled RCTs, typically 13 weeks in duration, to be effective in the treatment of acute exacerbations of schizophrenia (Gopal et al., 2010; Nasrallah et al., 2010; Pandina et al., 2010). In a fourth placebo-controlled RCT, paliperidone was shown to be superior to placebo and well tolerated; onset of action was as early as day 4 (Alphs, Bossie, Sliwa, Ma, & Turner, 2011). One longer-term RCT compared paliperidone palmitate (N = 379) to risperidone LAI (N = 370), finding that clinical improvement was greater in risperidone LAI compared to paliperidone palmitate, although this difference was thought to be due to suboptimal dosing of paliperidone (Fleischhacker et al., 2011). In a 52week open-label extension study with 388 patients, patients continued on paliperidone continued to improve clinically, with 74% completing the study, and the drug was tolerated with few adverse effects (insomnia, 7%; worsening of schizophrenia, nasopharyngitis, headache, and weight increase, 6% each; potentially prolactin-related adverse events, n = 13, 3%; extrapyramidal treatment-emergent adverse events, n = 25, 6%) (Gopal et al., 2011). In another study, data including 160 patients in a variable-duration, double-blind, randomized, relapse-prevention study followed by open-label extension in individuals with schizophrenia showed that hospitalizations decreased significantly for subjects receiving paliperidone palmitate as compared to the period before starting the medication (Kozma et al., 2011).

Lurasidone

Lurasidone is an antipsychotic that was approved for use in schizophrenia in 2010. It has been studied primarily in short-term (6 weeks) RCTs in acute schizophrenia. It has been shown to be superior to placebo at 40 mg, 80 mg, and 120 mg (Meltzer et al., 2011; Nakamura et al., 2009; Nasrallah et al., 2013; Ogasa, Kimura, Nakamura & Guarino, 2013). Lurasidone has also been compared to treatment with olanzapine (15 mg) in one of the aforementioned studies (Meltzer et al., 2011) and quetiapine extended-release (600 mg) in another (Loebel et al., 2013), and no differences in effectiveness as measured by PANSS and CGI were noted, although Meltzer and colleagues noted that dose-related akathisia was more common with lurasidone than with olanzapine.

In a 3-week, double-blind RCT, switching to lurasidone 120 mg in chronic and stable schizophrenia and schizoaffective disorder from other antipsychotic medications was as safe as switching to ziprasidone 80 mg twice daily, and both were associated with improvements in PANSS and small reductions in weight and cholesterol, although no changes were noted in triglycerides or electrocardiogram (Potkin, Ogasa, Cucchiaro, & Loebel, 2011). Similarly, in another 6-week RCT, cross-titration to lurasidone was well tolerated (McEvoy et al., 2013). Longer-term treatment with lurasidone was well tolerated and led to further improvements in PANSS in a 6-month open-label study with 254 patients who had started the study (Stahl et al., 2013). Similarly, continuation of flexibly dosed lurasidone in a 12-month, double-blind, noninferiority study in patients with chronic schizophrenia showed that lurasidone was not inferior to quetiapine extended-release with respect to relapse prevention and was superior with respect to the probability of hospitalization and remission rate (Loebel et al., 2013).

Iloperidone

Iloperidone is an SGA approved for the treatment of schizophrenia since 2009. It has been shown to be superior to placebo in the treatment of acute schizophrenia in doses ranging from 4 to 24 mg/day in at least four RCTs with a total of 2,536 patients (Cutler, Kalali, Weiden, Hamilton & Wolfgang, 2008; Potkin, Litman, Torres, & Wolfgang, 2008). Patients on iloperidone had lower rates of adverse events than those on ziprasidone (Cutler et al., 2008). In another RCT with 473 patients, EPS scores were noted to improve with iloperidone and worsen with the comparator haloperidol (Kane, Lauriello, Laska, Di Marino, & Wolfgang, 2008). Finally, a randomized open-label, multicenter study noted that iloperidone twice daily produced mean QTc changes similar to ziprasidone and higher than quetiapine, with once-daily dosing of iloperidone leading to QTc changes higher than ziprasidone.

Asenapine

Asenapine, which is taken as a sublingual tablet that dissolves under the tongue, was approved by the FDA in 2009. Asenapine has been shown to be superior to placebo in two 6-week RCTs with a total of 630 patients (Kane, Cohen, Zhao, Alphs, & Panagides, 2010; Potkin, Cohen, & Panagides, 2007). In a 26-week open-label study followed by a 26-week RCT in which patients were either continued on asenapine or switched to placebo, time to relapse/impending relapse and discontinuation for any reason were significantly longer with asenapine than with placebo, and incidence of relapse/impending relapse was lower with asenapine than placebo (12.1% vs 47.4%) (Kane et al., 2011). Asenapine was also studied in a 26-week RCT with a 26-week extension and noted to be inferior to the comparator olanzapine in terms of clinical effectiveness, EPS adverse events, and treatment discontinuation rates (Buchanan et al., 2012). The results were fairly consistent with another double-blind 1-year trial with 1,219 patients with schizophrenia and schizoaffective disorders in which asenapine patients, in comparison to olanzapine patients, exhibited lower trial completion rates, inferior clinical improvement, and greater EPS, although weight gain was greater with olanzapine (Schoemaker, Naber, Vrijland, Panagides, & Emsley, 2010). However, in another variable-length blinded extension study after a 52-week RCT in 440 schizophrenia and schizoaffective disorder patients, adverse events were lower in the extension than in the core study; body weight increase and incidence of EPS adverse events were negligible during extension; and clinical improvement was similar between asenapine and olanzapine (Schoemaker et al., 2012). Asenapine was also shown in an RCT to cause minimal change in QTc, similar to quetiapine (Chapel et al., 2009).

Summary of Meta-Analyses of Efficacy and Tolerability of Second-Generation Antipsychotics

In addition to meta-analyses for individual SGAs referenced earlier, several rigorous meta-analyses have been published (Davis, Chen, & Glick, 2003; Geddes, Freemantle, Harrison, & Bebbington, 2000; Leucht, Pitschel-Walz, Abraham, & Kissling, 1999; Leucht, Wahlbeck, Hamann, & Kissling, 2003) about the relative efficacy and safety/tolerability of SGAs compared with FGAs, and compared with other SGAs. In general, the studies included in these meta-analyses were conducted mostly in patients with an acute exacerbation, did not include treatment-resistant patients, were of relatively short duration, and assessed limited efficacy and safety outcome measures. Results have been variable, with some meta-analyses finding superiority of SGAs to FGAs with respect to efficacy and EPS liability (Leucht et al., 1999), others finding superiority of SGAs only with respect to efficacy but not tolerability (Davis et al., 2003; Leucht et al., 2003), and still others suggesting only slight superiority of SGAs with respect to tolerability but not efficacy (Geddes et al., 2000). A very recent meta-analysis, however, did note evidence of a continuum of efficacy of FGAs and SGAs, with the most effective antipsychotics on multiple different measures being SGAs (Leucht et al., 2013). At the present time the preponderance of the evidence suggests that while clozapine has superior efficacy in treatment-refractory populations, antipsychotics do not otherwise clearly separate from one another with respect to efficacy. Adverse side effect profiles do, however, differ substantially among the various medications.

Impact on Cognitive Functioning of Second-Generation Antipsychotics

The superiority of SGAs in improving cognitive function in schizophrenia relative to FGAs is not well established. Iatrogenic impairments in cognitive test performance in patients on the older drugs may result from EPS, anticholinergic effects, and sedative effects (Green & Braff, 2001; Mortimer, 1997; Velligan & Miller, 1999). The improvement reported in cognitive functioning with the SGAs relative to conventional agents may at least in part be attributable to elimination or relative reduction of some of these deleterious effects of FGAs. In general, patients on SGAs have demonstrated improvement in verbal fluency, digit symbol substitution, executive function, and fine-motor control (Green et al., 1997; Meltzer & McGurck, 1999). A large long-term RCT with 533 patients suggested the superiority of risperidone to haloperidol with respect to improvement in cognitive symptoms in first-episode patients (Harvey, Rabinowitz, Eerdekens, & Davidson, 2005), a 12-week RCT in 35 schizophrenia patients suggested superiority of olanzapine (Lindenmayer, Khan, Iskander, Abad, & Parker, 2007), and a meta-analysis by Keefe, Silva, Perkins, and Lieberman (1999) found a significant overall advantage for atypical antipsychotics on cognitive test performance. However, many studies have found no advantage for SGAs over FGAs. The CATIE trial noted similar cognitive improvements at 8 weeks between the two classes. Another RCT noted improvement in cognition at 12 and 52 weeks, with no differences between antipsychotics (Keefe et al., 2007), and other studies similarly found no differences (Green et al., 2002; Keefe et al., 2004, 2006). Furthermore, in one RCT with 188 patients, neurocognitive improvements in patients with schizophrenia and healthy controls were similar at 2 months, suggesting a practice effect (Goldberg et al., 2007). Overall, there is inconsistent evidence that antipsychotics lead to mild improvements in cognitive functioning, and there is no clear evidence that there is any difference between FGAs and SGAs with respect to cognitive improvement.

Clinical Antipsychotic Trials of Intervention Effectiveness

Many of the studies cited thus far, or used in meta-analyses, are of short-term duration and designed primarily for regulatory approval. Comparators are typically a placebo or a single fixed-dose active agent. Results are often not generalizable because the studies lack representative patient samples, clinical settings, and treatment conditions. The CATIE trial, funded by the National Institute of Mental Health, was a randomized comparison of the long-term effectiveness of olanzapine, risperidone, quetiapine, ziprasidone, and perphenazine (Stroup et al., 2003). The trial was designed to mimic clinical practice and was conducted between January 2001 and December 2004. It included approximately 1,500 patients with schizophrenia, using broad inclusion and minimal exclusion criteria, from 57 community sites, public health

systems, and academic settings. The primary outcome of CATIE was time to all-cause treatment discontinuation; secondary outcomes included discontinuation due to lack of efficacy, tolerability, patient decision, physician decision, psychopathology, safety, neurocognitive functioning, and cost-effectiveness. Patients in Phase 1 were initially randomly assigned to receive olanzapine (7.5 to 30 mg/day), perphenazine (8 to 32 mg/day), quetiapine (200 to 800 mg/day), or risperidone (1.5 to 6 mg/day) under double-blind conditions and followed for up to 18 months or until treatment was discontinued for any reason. Ziprasidone (40 to 160 mg/day) was approved for use by the FDA after the study began and was added to the study in January 2002. Patients whose assigned treatment was discontinued could switch and receive other treatments in Phases 2 and 3. With the exception of additional antipsychotic agents, concomitant medications were permitted throughout the trial.

In Phase 1 of the study (Lieberman et al., 2005), olanzapine was found to be superior to risperidone and quetiapine in terms of the time to *all-cause* discontinuation. Olanzapine was not statistically superior to ziprasidone or to perphenazine in time to all-cause discontinuation after adjustments for multiple comparisons. The percentage of patients who discontinued their medications for any cause prior to 18 months ranged from 64% (olanzapine) to 82% (quetiapine), with an overall discontinuation rate of 74%. The time to the discontinuation of treatment for *lack of efficacy* was longer in the olanzapine group than in the perphenazine, quetiapine, risperidone, and ziprasidone groups; however, the difference between the olanzapine and ziprasidone groups was not significant after adjustment for multiple comparisons. Patients taking olanzapine had the lowest rate of hospitalization for an exacerbation of schizophrenia (11%) versus 15% to 20% for the other agents. Patients taking olanzapine showed the highest rate of discontinuation due to side effects (18%), whereas risperidone had the lowest rate (10%). More patients discontinued perphenazine because of extrapyramidal effects (8% vs. 2% to 4% for the other agents). Quetiapine was associated with a higher rate of anticholinergic effects than any of the other agents (31% vs. 20% to 25%). There were no significant differences among the groups in the incidence of EPS, akathisia, or movement disorders as reflected by either the Simpson-Angus Extrapyramidal Signs Scale or the AIMS Global Severity Scale. There were no substantially different effects of the medications on the corrected QT interval on electrocardiography, and no patients developed torsades de pointes. There were no significant differences among the groups in the incidence of new cataracts, suicide attempts, or suicidal ideation. There were few substantial differences among the groups in the rates or types of medications added during the study. Patients in the olanzapine and risperidone groups were the least likely to receive additional anxiolytic agents, and patients on perphenazine were most likely to receive anticholinergic drugs. Nine percent of patients discontinued olanzapine because of weight gain or metabolic effects versus a 1% to 4% discontinuation rate for patients taking the other four drugs. Patients in the olanzapine group gained more weight than patients in any other group, with an average weight gain of 2 pounds (0.9 kg) per month, whereas patients taking perphenazine and ziprasidone showed a small weight loss per month. A larger proportion of patients (30%) in the olanzapine group gained 7% or more of their baseline body weight, higher than patients taking any of the other agents (7% to 16%). Olanzapine was also associated with greater increases in glycosylated hemoglobin, glucose, total cholesterol, and triglycerides than the other study drugs after adjustment for the duration of treatment. Ziprasidone was the only medication associated with improvement in each of these metabolic variables. Only risperidone was associated with a substantial increase in prolactin levels. The main findings of Phase 1 were that perphenazine, a typical antipsychotic, was similar in effectiveness to risperidone, quetiapine, and ziprasidone and only modestly less effective than olanzapine, and that all drugs were associated with a high rate of discontinuation. Limitations included a dose of olanzapine that was higher than the maximum approved dose, which may have conferred an efficacy advantage to olanzapine, and the fact that patients with tardive dyskinesia (approximately 200) were not randomized to perphenazine for obvious ethical reasons. Because patients with tardive dyskinesia may be more resistant to treatment, the study design may thus have favored perphenazine.

In Phase 2 of the study, subjects who had discontinued their first assigned treatment were offered entry into one of two possible treatment arms. If the drug in Phase 1 was discontinued primarily due to efficacy failure, patients were offered entry to a randomized trial that would compare open-label clozapine

treatment with blinded treatment with an atypical antipsychotic not previously received in Phase 1 of the trial (McEvoy et al., 2006). Patients were randomly assigned to open-label treatment with clozapine ($n = 49$) or to blinded treatment with olanzapine ($n = 19$), quetiapine ($n = 15$), or risperidone ($n = 16$). Time until treatment discontinuation *for any reason* was the primary outcome measure and was significantly longer for clozapine (median = 10.5 months) than for quetiapine (median = 3.3 months) or risperidone (median = 2.8 months), but not for olanzapine (median = 2.7 months). Time to discontinuation because of *inadequate therapeutic effect* was significantly longer for clozapine than for olanzapine, quetiapine, or risperidone. At 3-month assessments, PANSS total scores had decreased more in patients treated with clozapine than in patients treated with quetiapine or risperidone but not olanzapine. Thus, for these patients with schizophrenia who prospectively failed to improve with an atypical antipsychotic, clozapine was more effective than switching to another atypical antipsychotic. These advantages for clozapine were strong enough to achieve statistical significance despite the small sample sizes (McEvoy et al., 2006) and to underscore the superior therapeutic effect of clozapine in treatment-resistant populations.

In the other arm of Phase 2 (Stroup et al., 2006), subjects ($N = 444$) who had discontinued the first atypical antipsychotic due to either inadequate therapeutic effect or tolerability issues in Phase 1 of the CATIE investigation were randomly reassigned to double-blind treatment with a different atypical antipsychotic (olanzapine, 7.5 to 30 mg/day [$n = 66$]; quetiapine, 200 to 800 mg/day [$n = 63$]; risperidone, 1.5 to 6.0 mg/day [$n = 69$]; or ziprasidone, 40 to 160 mg/day [$n = 135$]). The time to treatment discontinuation was longer for patients treated with risperidone (median, 7.0 months) and olanzapine (6.3 months) than with quetiapine (4.0 months) and ziprasidone (2.8 months). There were no differences in the incidence of EPS among the drugs as reflected by rating scale measures of severity or reasons for discontinuing treatment. Patients receiving olanzapine gained more weight than did patients receiving any of the other drugs, with a mean of 1.3 pounds per month. Patients receiving ziprasidone had a mean loss of 1.7 pounds per month. Those receiving risperidone and quetiapine had negligible mean changes in weight over the course of Phase 2. Olanzapine was associated with substantial increases in total cholesterol and triglycerides, whereas risperidone and ziprasidone were associated with decreases in these parameters, even after adjusting for drug exposure. Patients receiving risperidone experienced substantial increase in prolactin levels and higher rates of adverse effects involving sexual functioning (29%) relative to the other groups (11% to 17%). Risperidone was also associated with higher rates of gynecomastia or galactorrhea (5%) relative to the other groups (less than 1%). More patients receiving quetiapine experienced orthostatic faintness (13%) relative to the other groups (4% to 7%). In summary, both risperidone and olanzapine were superior to quetiapine and ziprasidone on the primary outcome measure in this group of patients with chronic schizophrenia who had discontinued previous therapy with a different atypical antipsychotic.

Summary of Safety and Tolerability of Second-Generation Antipsychotics

The biggest advance in the side-effect profile of SGAs is the lower risk of acute EPS. Among the types of EPS, acute dystonia is very rare, whereas akathisia still occurs, albeit to a lesser degree, with perhaps lurasidone and asenapine being the most likely to cause akathisia. Within the group, clozapine and quetiapine have the lowest (almost absent) risk of parkinsonism, whereas risperidone, paliperidone, iloperidone, and, to a lesser extent, olanzapine, lurasidone, and asenapine are associated with dose-related parkinsonism. Ziprasidone and aripiprazole can also occasionally induce EPS, although it is not clear whether there is a dose relationship with these drugs. Lower rates of tardive dyskinesia have also been reported with risperidone compared with haloperidol (0.6% vs. 4.1%, respectively) in a 1-year double-blind study (Csernansky et al., 2002), and for olanzapine (Beasley et al., 1999) compared with haloperidol (0.5% vs. 7.4%, respectively). A review of eleven long-term studies of SGAs by Correll, Leucht, and Kane (2004) supported a lower risk of tardive dyskinesia for SGAs as a group compared with FGAs.

Weight gain has emerged as a major problem with some of the SGAs (Newcomer, 2005). Olanzapine and clozapine are most notorious in this respect, and in some patients rapid and massive weight gain can occur. Quetiapine, risperidone, paliperidone, and iloperidone are intermediate in weight gain liability, and

ziprasidone, aripiprazole, lurasidone, and asenapine rarely cause significant weight gain (Newcomer, 2005). Weight gain in patients with schizophrenia is especially problematic because these patients are usually overweight at baseline, have high rates of smoking, and are usually physically inactive. This combination of risk factors along with an increased risk of glucose dysregulation and hyperlipidemia reported to varying degrees with these agents (Newcomer, 2005) can create a potentially fatal constellation of risk factors for cardiovascular disease and stroke. These adverse effects, in their entirety, may well be worse than tardive dyskinesia, which was the primary concern for the older antipsychotics (Casey et al., 2004). The diabetes risk appears to be greatest for clozapine and olanzapine, less for risperidone and quetiapine, and lowest for ziprasidone and aripiprazole (Newcomer, 2005). Risperidone causes sustained prolactin elevation, and therefore patients who previously developed prolactin-induced side effects (galactorrhea, gynecomastia, menstrual irregularities, and sexual dysfunction) on older agents should probably be tried first on one of the other atypical antipsychotics. Ziprasidone is associated with QT prolongation, although the significance of this is not clear because related adverse events have not materialized after 5 years of clinical use. Iloperidone is associated with similar levels of QT prolongation to ziprasidone. Clozapine, in addition to agranulocytosis risk, is associated with significant orthostasis, tachycardia, seizures (dose-related), myocarditis, constipation (at times severe), and various other side effects, making it a challenging drug to use in clinical practice.

OTHER PHARMACOLOGICAL TREATMENTS

Because of the limited efficacy of antipsychotic medication in resolving the full range of schizophrenic psychopathology, and the frequently occurring comorbid symptoms that occur over the course of the illness (e.g., anxiety, depression, mood lability, and motor unrest), adjunctive treatments are often used to reduce morbidity. In the next section we review controlled trials of pharmacological agents other than antipsychotic medications that have been used to treat patients with schizophrenia. We report on the efficacy of these drugs when used either in combination with an antipsychotic drug or as a lone treatment, to treat both schizophrenic psychopathology and comorbid conditions. The classes of medication described are antianxiety/hypnotics, antidepressants, mood stabilizers, dopamine agonists, and glutamatergic agents. In addition, we briefly review the efficacy of electroconvulsive therapy as a treatment for schizophrenic psychopathology. The use of adjunctive pharmacological treatments in schizophrenia patients has been the subject of numerous reviews (Christison, Kirch, & Wyatt, 1991; Donaldson, Gelenberg, & Baldessarini, 1983; Johns & Thompson, 1995; Lindenmayer, 1995; Meltzer, 1992; Meltzer, Sdommers, & Luchins, 1986; Rifkin, 1993; Siris, 1993; Wolkowitz, 1993). Given our space limitations, and the large number of studies involved, where applicable, recent review articles are summarized and updated with reports of subsequently published methodologically rigorous studies.

Benzodiazepines

Benzodiazepines have been used to treat patients with schizophrenia since the early 1960s. Wolkowitz and Pickar (1991) reported that 9 of 14 studies using benzodiazepines alone to treat schizophrenic psychopathology showed significant improvement, whereas 11 of 16 studies using antipsychotic and adjunctive benzodiazepine showed utility of the adjunctive treatment. Benzodiazepines have also been compared with antipsychotics and a combination of both classes of drugs in the management of acute agitation and psychosis in acutely relapsed patients over the first few hours or days, and there is evidence from RCTs that benzodiazepines both alone and in combination with antipsychotics reduce aggression, agitation, and assaultive behavior (Barbee, Mancuso, Freed, & Todorov, 1992; Salzman et al. 1991), and benzodiazepine augmentation may be useful in limiting the quantity of antipsychotics used for the acute treatment of schizophrenia (Bodkin, 1990). Battaglia and colleagues (1997) conducted a prospective, randomized, double-blind, multicenter trial of 98 psychotic, agitated, and aggressive patients comparing lorazepam treatment, haloperidol treatment, and combination treatment. All three treatments were effective in achieving significant reductions in scores on the Agitated Behavior Scale after 1 hour and in a modified Brief Psychiatric Rating Scale after 2 and 3 hours, with combination treatment of lorazepam and haloperidol superior to either alone.

Another RCT with 53 patients with schizophrenia provided some evidence that diazepam, when given for indications of disturbed sleep, increased anxiety or other dysphoric affect, agitation and irritability, increased suspiciousness, and peculiar perceptual experiences thought to be prodromal of an impending psychotic exacerbation, was superior to placebo and comparable to fluphenazine in preventing a psychotic relapse (Carpenter, Buchanan, Kirkpatrick, & Breier, 1999). Indeed, there is some evidence to suggest that schizophrenia patients with anxiety, depression, hostility, irritability, and motor unrest may benefit from benzodiazepines (Kellner, Wilson, Muldawer, & Pathak, 1975; Wolkowitz & Pickar, 1991). Despite the evidence of benefits in some patients, there are reports that benzodiazepines may result in a "disinhibiting" effect (Karson, Weinberger, Bigelow, & Wyatt, 1982) or worsening of psychopathology in some patients (Wolkowitz & Pickar, 1991). Nevertheless, benzodiazepines appear to be useful adjuncts to antipsychotics in the treatment of agitation or anxiety, especially during acute psychotic relapse, as well as in managing the prodromal symptoms of an impending psychotic exacerbation.

Antidepressants

The efficacy of antidepressant medication for the treatment of schizophrenic psychopathology, used either alone or as adjuncts to antipsychotics, was first comprehensively reviewed by Siris, Van Kammen, and Docherty (1978) in an analysis of the results of double-blind, controlled studies. Their review suggested little utility in the use of antidepressants to treat schizophrenic psychopathology, although they cautioned that the overwhelming preponderance of negative findings might have resulted from weaknesses in study design, in particular inadequate antidepressant dosages. There is some evidence from RCTs that antidepressants (tricyclics were used in most but not all of the studies) are effective in relieving depressive symptoms (Hogarty et al., 1995; Plasky, 1991; Siris, 1991) and negative symptoms (Silver, Barash, Aharon, Kaplan, & Poyurovsky, 2000; Silver & Nassar, 1992; Siris, Pollack, Bermanzohn, & Stronger, 2000) outside of acute exacerbations, with some evidence that antidepressants may worsen psychosis during acute exacerbations (Plasky, 1991). Berk, Ichim, and Brook (2001) conducted a 6-week randomized, placebo-controlled trial of mirtazapine and haloperidol versus placebo and haloperidol in 30 patients with schizophrenia and found clinical improvement in negative symptoms but not depressive symptoms. In a meta-analysis of seven randomized controlled trials ($N = 202$), the combination of antidepressants and antipsychotics was suggested to be superior to antipsychotics alone in the treatment of negative symptoms (Rummel, Kissling, & Leucht, 2005). One long-term RCT suggested the utility of antidepressant treatment in preventing relapse of patients with schizophrenia or schizoaffective disorder into either depression or psychosis (Siris, Bermanzohn, Mason, & Shuwall, 1994). Overall, the available data suggest that adjunctive antidepressant treatment is warranted when a patient reports persistent symptoms of depression when not in an acute episode of his or her illness, and for those with prominent negative symptoms.

Mood Stabilizers

Lithium

Lithium salts have been used both alone and as an adjunct to antipsychotics in the treatment of schizophrenia patients (Atre-Vaidya & Taylor, 1989; Christison et al., 1991). Atre-Vaidya and Taylor (1989) reported on three small studies (Carman, Bigelow, & Wyatt, 1981; Growe, Crayton, Klass, Evans, & Strizich, 1979; Small, Kellams, Milstein, & Moore, 1975) that examined lithium as an adjunct to antipsychotics for treatment-refractory patients and found greater improvement with adjunctive lithium compared with antipsychotics alone. Most later studies, however, find no utility of adjunctive lithium in treating psychotic symptoms in patients with schizophrenia (Hogarty et al., 1995; Schulz et al., 1999; Small, Klapper, Malloy, & Steadman, 2003; Terao et al., 1995; Wilson, 1993), although there is some evidence that some patients with schizoaffective disorder with inadequate response to antipsychotic medication alone may achieve greater symptom reduction with adjunctive lithium (Schulz et al., 1999; Small et al., 2003). Not surprisingly, in a more recent meta-analysis (Leucht, Kissling, & McGrath, 2004) that included 20 controlled studies of lithium alone or as an augmentation agent in treatment of schizophrenia/schizoaffective disorder, it was found that lithium as a sole agent was ineffective, and as an

augmentation strategy it was effective only in patients with prominent affective symptoms.

In summary, most of the available literature suggests that in the absence of affective symptoms, augmentation of antipsychotics with lithium is not effective in the treatment of schizophrenia. However, because there have been reports of a benefit in some treatment-refractory patients, a trial of lithium should be considered if the patient has not adequately responded or was unable to tolerate clozapine. Earlier concern about potentially toxic interactions between an antipsychotic and lithium (Cohen & Cohen, 1974) appears not to be supported by the vast majority of the published literature (Rifkin, 1993). However, patients co-administered lithium and clozapine may be at higher risk of neurotoxicity.

Carbamazepine

Christison and colleagues (1991) reviewed five double-blind studies published through 1989 in which either carbamazepine or placebo was added to a stable antipsychotic regimen and found modest positive results in three. Leucht, Wahlbeck, Hamann, and Kissling (2003) reviewed 10 RCTs (N = 283) comparing carbamazepine (as a sole or an adjunctive compound) and found no benefit from monotherapy or adjunctive treatment with carbamazepine. Overall, there is some evidence to support carbamazepine as an adjunctive agent to antipsychotics in the treatment of schizophrenia, particularly in a subpopulation of aggressive, agitated patients. Due to carbamazepine's ability to upregulate hepatic enzymes, plasma antipsychotic levels may drop with concomitant carbamazepine use, requiring antipsychotic dose adjustment.

Valproic Acid

Valproic acid as an adjunct to antipsychotics has been the focus of a few controlled studies. While two small RCTs have shown benefit in terms of psychopathology with adjunctive valproic acid (Linnoila, Viukari, & Kietala, 1976; Wassef et al., 2000), other RCTs, including a large RCT with 249 patients with schizophrenia, have shown no benefit at study endpoint (Casey et al., 2003; Ko, Korpi, Freed, Zalcman, & Bigelow, 1985), although there may be some early benefit in terms of reducing hostility. Basan, Kissling, and Leucht (2004) conducted a meta-analysis of five (N = 379) RCTs comparing valproate as an adjunctive compound for patients with schizophrenia or schizophrenia-like disorders and found no overall superiority of valproate augmentation at study endpoints. Overall, the preponderance of the evidence suggests that valproic acid is not useful in the treatment of schizophrenia.

Dopamine Agonists

Dopamine agonists have been associated with an exacerbation of psychotic symptoms in 40% to 60% of schizophrenia patients; however, these agents have also been used as a treatment for patients with prominent negative symptoms. This strategy is consistent with the hypothesis that a hypodopaminergic state is responsible for the negative symptoms of the illness (Davidson et al., 1991). The efficacy of L-dopa has been assessed in three small, low quality, double-blind treatment studies (Christison et al., 1991; Brambilla et al., 1979), two of which used it as an adjunct to antipsychotics (Gerlach & Luhdorf, 1975; Inanaga et al., 1975). These studies suggested possible utility of L-dopa in treating negative symptoms in particular.

Other dopamine agonists have been studied with inconsistent results in RCTs suggesting no utility of adjunctive bromocriptine (Gattaz, Rost, Hubner, & Bauer, 1989) or mazindol, a dopamine reuptake inhibitor (Carpenter et al., 2000), some affective and cognitive benefit of a single dose of dextroamphetamine (Barch & Carter, 2005; Goldberg, Bigelow, Weinberger, Daniel, & Kleinman, 1991), and minimal to moderate improvement on negative and other symptoms with adjunctive selegiline (Jungerman, Rabinowitz, & Klein, 1999). Dopamine agonists have been the subject of too few controlled studies to allow us to draw definitive conclusions, and the above studies do not suggest clear utility of these medications, although clinicians' hesitancy to use these agents due to concern about exacerbating psychotic symptoms may not be warranted if patients are maintained on antipsychotics (Perovich, Lieberman, Fleischhacker, & Alvir, 1989).

Glutamate Agonists

Phencyclidine was first observed by Luby, Cohen, Rosenbaum, Gottlieb, and Kelly (1959) to produce a syndrome similar to schizophrenic psychosis with its

associated emotional withdrawal, apathy, and cognitive impairment. A later study by Anis and colleagues (1983) demonstrating that phencyclidine blocks the N-methyl-D-aspartic acid (NMDA) subtype of the glutamate receptors in a noncompetitive manner led to an intensified effort to understand the role of glutamate receptors in schizophrenia. Because phencyclidine inhibits the neurotransmission of glutamate through NMDA receptors (i.e., is an NMDA antagonist), it was hypothesized that reduced glutamate activity (possibly through NMDA receptor hypofunction) caused the symptoms of schizophrenia (Javitt & Zukin, 1991), and from this hypothesis it was inferred that agents that facilitate the stimulation of NMDA receptors would be therapeutic in schizophrenia. In this context, four glutamate agonists have been studied to date: glycine, D-cycloserine, D-serine, and sarcosine (Table 6.3).

Seven double-blind studies have evaluated the use of glycine as an adjunctive treatment to antipsychotic medications, with some studies suggesting benefit of adjunctive low-dose glycine (15 g/day) with respect to psychiatric symptoms (Potkin et al., 1992); others suggesting improvement in negative symptoms at 30 g/day of adjunctive glycine (Javitt, Zylberman, Zukin, Heresco-Levy, & Lindenmayer, 1994) or improvement in negative, depressive, or cognitive symptoms at up to 60 g/day of adjunctive glycine (Heresco-Levy et al., 1996, 1999; Heresco-Levy, Ermilov, Lichtenberg, Bar, & Javitt, 2004); and still others failing to show any benefit (Evins, Fitzgerald, Wine, Rosselli, & Goff, 2000; Potkin, Jin, Bunney, Costa, & Gulasekaram, 1999). Despite some encouraging results, glycine is known to have poor central nervous system bioavailability, and the doses needed to effect clinical benefit (30 to 60 g/day) are very difficult to administer.

D-cycloserine (DCS) freely crosses the blood–brain barrier and acts as a partial agonist at the glycine regulatory site on the NMDA receptor. Because of this latter feature, DCS stimulates NMDA receptor function at low doses but inhibits endogenous glycine activity

TABLE 6.3 Glutamate Agonists

Drug	*Positive vs. Negative Results*	*Author*	*Comments*
Glycine	Positive	Potkin et al. (1992) Javitt et al. (1994) Heresco-Levy et al. (1996) Heresco-Levy et al. (1999) Heresco-Levy et al. (2004)	Poor central nervous system bioavailability; doses needed to for clinical benefit (30–60 g/day) difficult to administer
	Negative	Potkin et al. (1999) Evins et al. (2000)	
D-cycloserine	Positive	Goff et al. (1999) Evins et al. (2002) Gottlieb et al. (2011)	Narrow therapeutic range; outside of this range, D-cycloserine is at best not effective, at worst may worsen psychosis
	Negative	Goff et al (1995) Rosse et al. (1996) Evins et al. (2002) Buchanan et al. (2007) Goff et al. (1999)	
D-serine	Positive	Tsai et al. (1998) Heresco-Levy et al. (2005) Lane et al. (2010)	Full NMDA agonist with greater central nervous system bioavailability than glycine
	Negative	Tsai et al. (1999) Gottlieb et al. (2011)	
Sarcosine (N-methylglycine)	Positive	Tsai et al. (2004) Lane et al. (2005)	Endogenous antagonist of glycine transporter-1, which potentiates glycine's action
	Negative	N/A	

at higher doses, thus lowering NMDA receptor function. There is some evidence from RCTs that the drug is effective in treating negative symptoms in a narrow therapeutic range when added to FGA regimens (Evins, Amico, Posever, Toker, & Goff, 2002; Goff et al., 1999b), but other RCTs have established that very low or high doses are either not effective or may worsen psychosis (Evins et al., 2002; Goff et al., 1995; Rosse, Fay-McCarthy, Kendrick, Davis, & Deutsch, 1996). Notably, however, a more recent study has suggested that DCS can help facilitate cognitive-behavioral therapy for delusions in schizophrenic patients by reducing delusional distress and severity if given before starting cognitive-behavioral therapy (but not halfway through) (Gottlieb et al., 2011). Despite early evidence that adjunctive DCS was effective in treating negative symptoms within a narrow therapeutic range, some large, high-quality RCTs have had negative results (Buchanan et al., 2007), and adjunctive DCS did not improve symptoms when added to clozapine treatment (Goff, Henderson, Evins, & Amico, 1999a).

Another glutamate agonist candidate for the treatment of schizophrenia is D-serine (DS), which is a full NMDA agonist with greater central nervous system bioavailability than glycine. A study by Tsai, Yang, Chung, Lange, and Coyle (1998) evaluated the use of DS in 29 patients (25 treated with FGAs and 4 treated with risperidone) with deficit syndrome schizophrenia and found improvements in positive, negative, and cognitive symptoms. In a later add-on study of clozapine, Tsai and colleagues (1999) found that symptoms did not improve with adjunctive DS. In a double-blind, placebo-controlled, 6-week crossover trial with DS 30 mg/kg per day added to the antipsychotic medication of 39 patients with schizophrenia (21 on risperidone and 18 on olanzapine), DS administration resulted in significant improvements in negative, positive, cognitive, and depression symptoms (Heresco-Levy et al., 2005). The results for more recent studies have been conflicting, with one RCT showing add-on of DS (30, 60, and 120 mg/kg) leading to significant improvement in PANSS positive, negative, total, and general symptoms, and on the MATRICS composite score at higher doses (60 mg/kg or more) (Lane et al., 2010), whereas another RCT with 195 patients found no effect of 2 g/day DS as adjunctive therapy to antipsychotics (Gottlieb et al., 2011), possibly limited by low dosing.

The glycine transporter-1 is a novel target for the pharmacotherapy to enhance NMDA function. Inhibition of the glycine transporter-1 would be expected to increase synaptic glycine levels and augment NMDA receptor function. N-methylglycine (sarcosine) is an endogenous antagonist of glycine transporter-1, which potentiates glycine's action on the NMDA glycine site, and in one 6-week RCT with 38 patients, sarcosine as an add-on to antipsychotics (mostly risperidone) led to significant improvement in positive, negative, cognitive, and general psychiatric symptoms and was well tolerated (Tsai, Lane, Yang, Chong, & Lange, 2004). Lane, Chang, Liu, Chiu, and Tsa (2005) conducted a 6-week randomized, double-blind, placebo-controlled trial to determine whether DS (2 g/day) or sarcosine (2 g/day) had better efficacy when added to risperidone treatment in 65 patients with acute exacerbation of schizophrenia. The sarcosine group was superior to both the placebo and DS groups in improvement in PANSS total scores, Scale for the Assessment of Negative Symptoms (SANS) scores, PANSS depressive, and PANSS general subscales. Unlike other studies that have found a benefit for DS, in this study adjunctive DS with risperidone did not differ significantly from risperidone monotherapy in all efficacy domains.

Glycine, DCS, DS, and sarcosine all show some benefit for the treatment of negative, cognitive, and psychotic symptoms when dosed appropriately. Although dosing challenges with glycine and DCS may make them impractical for clinical use, studies with these compounds provide strong support for the role of glutamate in the pathophysiology of schizophrenia, as well as furthering the understanding of the unique pharmacological mechanism of clozapine. DS is the most promising agent in this group based on the current findings. This line of research will, we hope, lead to improved symptom reduction for patients with schizophrenia and clues leading to the development of other novel therapeutic agents.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT), which was an acceptable treatment option for schizophrenia before the introduction of antipsychotic medication, has been the subject of few controlled studies. Information gathered from open trials suggests that ECT works best in schizophrenia patients in the early stages of their illness, in those with catatonic or affective symptoms, and in conjunction with an antipsychotic (Salzman, 1980). ECT is rarely used in the

treatment of schizophrenia patients today except in the most refractory cases.

Three double-blind, controlled studies of schizophrenia patients maintained on antipsychotics who received either ECT or sham ECT have produced consistent results. These studies, each with approximately 20 patients treated with antipsychotics augmented by ECT or sham treatment, found evidence of more rapid early improvement that disappeared at later time points (Abraham & Kulhara, 1987; Brandon et al., 1985; Taylor & Fleminger, 1980). Interestingly, May and colleagues (1981), in a 5-year prospective study of 228 first-episode schizophrenia patients who received one of five treatments by random assignment (antipsychotics, ECT, psychotherapy, psychotherapy plus antipsychotic, or milieu), found that the outcomes in all groups were poor, but that the ECT-treated group fared best.

Chanpattana, Chakrabhand, Buppanharun, and Sackeim (2000) conducted a double-blind comparison of three different stimulus intensities (seizure threshold, two times seizure threshold, and four times seizure threshold) of bilateral ECT plus flupenthixol in the treatment of 62 patients with schizophrenia. They concluded that treatment with high-dosage bilateral ECT speeds clinical response in patients with schizophrenia. Chanpattana and colleagues (1999) compared flupenthixol alone, continuation ECT alone, and combined continuation ECT and flupenthixol in a 6-month single-blind study of 58 patients with treatment-resistant schizophrenia who had met response criteria after an acute phase of treatment with bilateral ECT and flupenthixol (12 to 24 mg/day). Patients treated with the combination of bilateral ECT and flupenthixol relapsed at a rate of 40% (6/15), whereas patients in the bilateral ECT-alone and flupenthixol-alone groups relapsed at a rate of 93% (14/15). All 8 of the patients treated with the combination of the two treatments maintained therapeutic benefits at follow-up of 3 to 17 months.

Tharyan and Adams (2005) reviewed 26 RCTs that compared ECT with placebo (sham ECT), nonpharmacological interventions, and antipsychotics for people with schizophrenia, schizoaffective disorder, or another chronic mental disorder. When ECT was compared with sham ECT, more people improved in the real ECT group ($N = 392$, 10 RCTs). There was no evidence that this early advantage for ECT was maintained over the medium to long term, however. When ECT was compared with antipsychotic drug treatments (total $N = 443$, 10 RCTs), results favored the medication group. Limited evidence suggested that ECT combined with antipsychotic drugs results in greater improvement in mental state ($N = 40$, one RCT) than with antipsychotic drugs alone. When continuation ECT was added to antipsychotic drugs, the combination was superior to the use of antipsychotics alone ($n = 30$) or continuation ECT alone ($n = 30$). Unilateral and bilateral ECT were equally effective in terms of global improvement ($N = 78$, two RCTs). One trial showed a significant advantage for 20 treatments over 12 treatments in terms of the number of patients manifesting global improvement at the end of the ECT course ($N = 43$). The authors concluded that the evidence suggested that ECT, combined with treatment with antipsychotic drugs, may be considered an option for people with schizophrenia, particularly when rapid global improvement and reduction of symptoms are desired, as well as for those with schizophrenia who show limited response to medication alone.

CONCLUSIONS

Pharmacological treatment has had a profoundly positive impact on the course of schizophrenia, with the vast majority of patients now no longer requiring chronic institutionalization. Nevertheless, schizophrenia remains a major public health concern, with patients over the course of their illness displaying varying degrees of social and vocational disability and remaining susceptible to psychotic exacerbations even when compliant with medication. A large number of high-quality studies in recent years have established that the clearest differentiation between FGAs and SGAs is with respect to tolerability rather than efficacy, although there are unequivocal data to suggest that clozapine is superior to other antipsychotics, particularly in treatment-resistant patients, and some evidence for an efficacy advantage of olanzapine as well. However, metabolic side effects have proven to be serious side effects of a number of the newer agents. It should also be noted that the importance of continuing long-term antipsychotics at doses that are efficacious during acute exacerbations during the relapse prevention phase has been established. Furthermore, although switching agents has been shown to be relatively safe, it has been associated with an increased risk of relapse, so the risks and

benefits should be weighed carefully when considering switching. There is some evidence for the use of adjunctive medications to treat other psychiatric symptoms in patients with schizophrenia. Although antipsychotics have been very effective in treating positive symptoms in many patients, they have been shown to be considerably less effective with respect to the treatment of cognitive and negative symptoms, and patients have thus remained relatively disabled in their everyday lives.

Accumulating evidence indicating the value of treating patients with schizophrenia as early in the course of the illness as possible, and reducing the duration of untreated psychosis has led to early detection and intervention strategies to optimally treat patients in their first acute episode of illness and potentially while in the prodromal phases. This strategy offers great hope for limiting the cumulative morbidity and disability of schizophrenia for future generations of patients. At the same time, continued efforts are being made to develop new treatments acting at novel targets that may have either superior antipsychotic efficacy or efficacy in treating cognitive and negative symptoms as well.

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7

Cognitive and Social Cognitive Interventions for Schizophrenia

Matthew M. Kurtz

Cognitive remediation (CR) and social cognitive training (SCT) are increasingly studied behavioral interventions for improving disorder-linked cognitive and social cognitive deficits in schizophrenia. They appear to hold considerable promise for improving disorder outcome. A synthetic, critical review of the extant literature on these treatments for schizophrenia revealed over 80 controlled studies on CR and 20 controlled studies on SCT. Results for both classes of interventions have been largely positive. Seven meta-analyses of CR and one meta-analysis of SCT have been conducted to date. Conclusions from the most recent meta-analysis of CR included 40 studies, the majority of which were type 1; the meta-analysis revealed moderate-sized effects on cognitive outcomes (d = .45) and measures of functioning (d = .42). Strongest effects of CR on functioning were evident when the intervention was paired with other psychosocial treatments. A meta-analysis consisting of 19 studies of SCT revealed moderate treatment effects on specific outcomes targeted by the interventions, including facial affect recognition (d = .71) and Theory-of-Mind (d = .46), as well as evidence of the extension of treatment effects to functioning (d = .78). While SCT has been one key element of effective, integrated programs of psychosocial intervention, only four type 1 studies using broad-based, sustained, standalone programs of SCT have been completed to date. Preliminary results are promising.

INTRODUCTION

As opposed to many of the treatment modalities discussed in this book, cognitive and social cognitive interventions for people with schizophrenia are (1) novel, emerging in a systematic manner only over the past 10 to 15 years, and (2) largely understudied to date. Thus, research on central questions regarding mechanisms of treatment action, whether treatment should be focused on compensatory training to create "workarounds" for existing deficits or employ strategies for improving deficits directly, and the science of who responds to these interventions and who doesn't is still in an inchoate state. Additional, important questions regarding how these interventions can be integrated most effectively with extant, evidence-based psychosocial and pharmacological practices in schizophrenia have been studied more, but the total number of studies still remains very small. Results of controlled and frequently randomized and blinded trials of cognitive remediation have been both impressive in individual studies and remarkably robust in their effects across studies, despite widely varying strategic treatment approaches, control conditions, duration of interventions, selection of outcome measures, sample characteristics, and adjunctive treatments, (e.g., McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Nonetheless, motivational deficits remain a key feature of the disorder and impede the ability of all people with the diagnosis to benefit equally from these treatments (Medalia & Richardson, 2005; Medalia & Saperstein, 2011). Controlled trials of social cognitive therapies,

while smaller in number, have shown considerable promise as well (e.g., Kurtz & Richardson, 2012). Cognitive and social cognitive therapies thus represent an exciting new frontier in the study of psychosocial treatment for schizophrenia. Their promise suggests a high probability of inclusion in the armamentarium of the next generation of interventions for the promotion of optimal recovery in schizophrenia.

COGNITIVE REMEDIATION

Cognitive remediation (CR) for schizophrenia was well defined at a meeting of the Cognitive Remediation Experts Workshop (Florence, Italy, April 2010) as "a behavioral training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or meta-cognition) with the goal of durability and generalization." CR for schizophrenia has seen a remarkable growth in research interest over the past 20 years. This growth can be seen in the rapidly accelerating cumulative number of controlled trials in the field and a 100% increase in the number of randomized trials over the past four years alone (Fig. 7.1).

Historical Antecedents

Cognitive Impairment in Schizophrenia

Emil Kraepelin and Eugen Bleuler, both widely considered to have formulated the first modern diagnostic conceptions of schizophrenia at the end of the 19th and beginning of the 20th centuries, described deficits in attention, memory, and other cognitive functions as a key feature of their newly defined disorder. Indeed, Kraepelin's first term for schizophrenia, described in the fifth edition of his clinical textbook *Psychiatry* in 1896, was *dementia praecox*, meaning literally a dementia with early onset (Kraepelin, 1920; Shorter, 1997). Similarly, Bleuler, who coined the term *schizophrenia*, thought that all manifestations of the disorder were secondary to four fundamental symptoms (the four As) of which one was *association*, or the appropriate linking of ideas. As Bleuler states:

> The schizophrenic is not generally demented but he is demented with regard to certain periods, to certain constellations, and to certain complexes. In mild cases, the defective functions are the exception. In most severe cases, those who sit around in our mental institutions taking no part in anything, the defective functions are the rule…The mildest case can commit as great a piece of folly as the most severe, but he commits it far more rarely. (pp. 73–74, E. Bleuler, 1950, *Dementia Praecox*)

Bleuler's ideas were particularly prescient in that they anticipated three key facts about cognitive deficits in schizophrenia: (1) they are a core feature of the disorder, (2) there is a great deal of heterogeneity in these deficits from person to person with the diagnosis, and (3) they are closely linked to functional outcome.

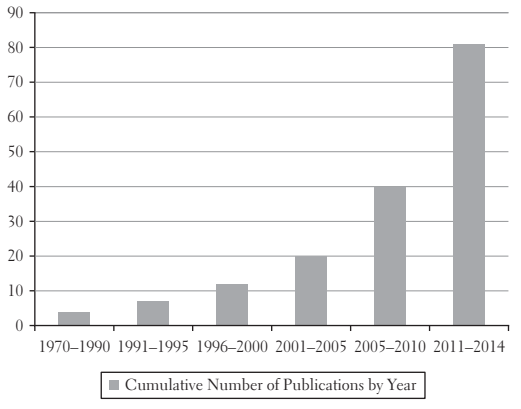

FIGURE 7.1 Cumulative number of controlled studies on cognitive remediation interventions in schizophrenia.

Cognitive Remediation in Schizophrenia

The two foundational studies in the study of CR in schizophrenia were motivated by theories regarding the role of behavioral reinforcement and cognition in the control of overt behavior in healthy populations. They presaged the importance of these factors in contemporary research for promoting strong outcomes in CR studies in schizophrenia. Wagner (1968) investigated the role of contingent reinforcement and task practice on several neurocognitive outcome measures, including measures of abstraction, vocabulary, and nonverbal memory, in eight individuals with schizophrenia. In a counterbalanced, within-subject design, results revealed that contingent reinforcement produced improvement in four of the five neurocognitive measures; these findings could not be accounted

for by simple task practice alone. Using a very different approach, Meichenbaum and Cameron (1973) evaluated the role of self-instructional training procedures, which consisted of verbalizing the nature and demands of a task, mentally rehearsing these demands to maintain task focus, and giving self-instruction and self-reinforcement to enhance both concentration and motivation for task performance, in a sample of hospitalized individuals with schizophrenia. Results revealed improvements in working memory, sustained attention, and processing speed greater in magnitude than repeated exposure to and practice with the cognitive outcome measures. Thus, both of these studies provided early evidence that a variety of cognitive deficits in people with schizophrenia were modifiable with appropriate training.

Neurocognition in Schizophrenia

Anecdotes describing superior intellectual function and singular creative accomplishment in people with schizophrenia abound and support the popular, socially constructed myth of the "mad genius." Probably the best example of this concept is expressed in the life of John Nash, the renowned Princeton mathematician, Nobel Prize winner, and focus of both a major biography and biographical film, *A Beautiful Mind*. Nash was diagnosed with schizophrenia in his 30s and likely developed major symptoms of the disorder, such as auditory hallucinations and crystallized delusions (which included beliefs that he was receiving coded messages from extraterrestrials through *The New York Times*), well before this time (Green, 2003). Despite such powerful case studies, a wealth of evidence conducted over the past 25 years has starkly contradicted these commonly held views about schizophrenia and revealed a broad range of substantial and persistent deficits in neurocognition.

It has been known for some time that IQ measures are, on average, lower in people with a diagnosis of schizophrenia than the general population (e.g., Aylward, Walker, & Bettes, 1984). Furthermore, deficits of a magnitude of one to two standard deviations relative to healthy controls are evident on both standardized clinical neuropsychological assessment tools and experimental psychopathological measures in the domains of attention, verbal and nonverbal memory, working memory, language, problem solving and inhibition, and sensory and motor skills, among others (e.g., Goldberg, David, & Gold, 2011; Heinrichs & Zakzanis, 1998). These deficits are evident in clinical high-risk states and thus presage the disorder. They are also seen in an attenuated form in first-degree relatives without the illness and without exposure to psychotropic medications (e.g., Cannon, Bearden, Hollister, Rosso, Sanchez, & Hadley, 2000), are evident at illness onset (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009), and persist through middle age and into senescence (Irani, Kalkstein, Moberg, & Moberg, 2011). Indeed, several recent studies suggest that virtually all people with schizophrenia have some level of cognitive impairment if levels of premorbid intellectual functioning are accounted for (Kurtz, Donato, & Rose, 2011) and the presence of cognitive impairment is more common than estimates of the presence of delusions that are frequently used to diagnose the disorder (Harrow & Jobe, 2010). These deficits persist in the face of optimal pharmacotherapy for positive symptoms, emphasizing the need for novel, adjunctive treatments (Green, Kern, Braff, & Mintz, 2000). For all of these reasons, neurocognitive deficits are viewed as a core feature of the disorder.

Neurocognition and Functional Status in Schizophrenia

A key rationale for the development and assessment of novel CR interventions in schizophrenia has been derived from research showing a substantial and well-replicated link between measures of neurocognitive skills and functional status in schizophrenia. These links became a fundamental concept in the field of schizophrenia research through a series of highly cited critical, integrative review papers by Michael Green and his colleagues at UCLA (Green, 1996; Green et al., 2000, Green, Kern, & Heaton, 2004). While these relationships had been noted in previous work (e.g., Heaton & Pendleton, 1981), the powerful influence of Green's reviews lay in the careful documentation of relationships among a wide range of indices of neurocognitive function. Those indices included sustained vigilance, verbal learning and memory, verbal fluency, concept formation and conceptual flexibility, psychomotor speed and elementary sensory processing, and a variety of domains of functional status in schizophrenia, including ratings from patient- and informant-reported

community function scales, laboratory-administered and performance-based measures of social and everyday adaptive life skills, and the measurement of progress in psychosocial rehabilitation programs. Indeed, across studies, cognition accounted for anywhere from 20% to 60% of the variance in these different indices of functional status, suggesting substantial overlap between these key disorder domains. These findings have been buttressed by (1) a growing body of longitudinal data that has linked cognitive skills in people with schizophrenia in similar stages of illness as predictors of functional status measured as long as a decade later (e.g., Stirling et al., 2003) and (2) increasing data suggesting that neurocognitive skills play an important, rate-limiting step in the acquisition of elementary social skills and work-related skills in work therapy and supported employment programs and in comprehensive outpatient therapy programs (Kurtz, 2011). These links provide support for the possibility that improving cognitive skills may improve outcome in the disorder. An important limitation of this rationale is that these relationships are correlative and additional variables could be playing important causative roles in these associations.

Methods of Cognitive Remediation

For the purposes of this chapter we divide CR approaches into four major intervention categories.

Strategy-based approaches focus on the acquisition of skills for circumventing cognitive difficulties. In most cases, in an approach that has been labeled *scaffolding*, the therapist will provide cognitive supports for a task at first. These supports are reviewed with the client, and then the client is allowed to practice cognitive strategies as the therapist gradually removes these supports. These approaches place considerable emphasis on verbally mediated coaching and extensive client–therapist interaction. A key value of this approach is that the skills taught are generalizable. Thus, training is tailored directly to cognitive skills used in everyday life tasks and often specific sessions will be devoted to applying skills. The best-studied version of this approach in the research literature is Cognitive Remediation Therapy (CRT; e.g., Wykes et al., 2007a, 2007b), developed by Til Wykes and her colleagues at the Institute of Psychiatry in London.

Restorative approaches target cognitive deficits directly through repeated task practice, careful titration of task difficulty, and maintenance of high levels of accurate performance. This approach can be likened to the approach of a physical therapist, prescribing consistent and sustained exercise for muscle groups that have atrophied due to disuse or structural damage. In these interventions task practice is typically organized hierarchically, with elementary aspects of sensory processing or attention trained first, followed by training in higher-order memory and problem-solving skills. These approaches often rest on the assumption that improvements in cognition are mediated by neural plasticity and lead to more accurate sensory representations of environmental stimuli, thereby enhancing the output of computational cognitive systems.

Motivational approaches usually consist of an admixture of both restorative drill-and-practice training and strategy acquisition as a technique for improving cognitive function. The specific training method is considered secondary to the promotion of an intrinsic motivational set that is evoked through careful attention to the learning environment, therapist approach, and training materials. It is this enhanced motivational set that leads to greater task engagement and improved outcomes by this approach.

Hybrid approaches typically offer treatment in neurocognitive skills along with a package of other skills training modules, including social cognition (the ability to accurately decode the mental states of others) and/or social skills (Kurtz, 2012).

For each class of intervention we describe both the methods used for improving cognitive function and the empirical basis for intervention efficacy.

Strategy-Based Cognitive Remediation Training

To date, the best-studied strategy-based remediation intervention has been CRT (Delahunty et al., 2002; Wykes et al., 2007a, 2007b). CRT is based on three key principles: (a) teaching new, efficient information-processing strategies; (b) individualizing therapy; and (c) aiding the transfer of cognitive gains to the real world. The program includes several modules: cognitive flexibility, working memory, and planning. Each module consists of a series of exercises graded from "extremely easy" to "easy" to minimize task-related errors and promote errorless learning. In the cognitive flexibility module clients

are given practice in engagement, disengagement, and reengagement with a particular cognitive task or between two tasks. The working memory module requires the person to maintain two sets of information simultaneously and to carry out cognitive operations on this retained information. The planning module consists of tasks in which the participant tries to achieve a goal by planning a series of preparatory moves. The emphasis in this module is to organize information and to create and use subgoals. Within each module information-processing strategies are incorporated into each task at first (e.g., performance speed on a task may be regulated by the therapist by pointing to each test item at a fixed rate). The information-processing strategy is then discussed with the client, who then practices the strategy with the therapist (e.g., slowing down performance speed) overtly and then covertly. CRT has shown effectiveness in the earliest phases of the illness (Wykes et al., 2007a), with evidence that the intervention effects persist over time (Wykes et al., 2003) and that improvements can be linked to improvements in work quality measures (Wykes et al., 2012).

In another example of strategy-based training, Twamley and colleagues (2008) have developed a manualized intervention that is unique in the field of compensatory training. It uses modules that combine internal (use of acronyms and visual imagery) and external supports (writing down lists, placing lists in a convenient and visible location in the home environment) in many instrumental everyday tasks identified as important by consumers, family members, and therapists. Skills training modules are grouped into four general domains of prospective memory, attention and vigilance, learning and memory, and executive function. The types of everyday tasks trained in the program include remembering to go to work or school (prospective memory), focusing attention in class (attention and vigilance), learning and remembering names of supervisors (learning and memory), and self-monitoring work performance (executive function). Results from a recent type I randomized controlled trial of this intervention with 69 chronic outpatients with schizophrenia showed positive effects of the intervention on measures of attention and verbal memory and performance-based measures of function (e.g., writing a check, planning a trip to the beach), as well as negative symptoms and quality of life, relative to a control group treated with routine pharmacotherapy (Twamley, Vella, Burton, Heaton, & Jeste, 2012).

Restorative Cognitive Remediation Training

Two restorative CR programs have been studied most intensively to date: Neurocognitive Enhancement Therapy (NET), developed by Wexler, Bell, and their colleagues, and the PositScience Brain Fitness program, which has been evaluated in a series of randomized controlled trials by Sophia Vinogradov and her colleagues. Both are computer-assisted, hierarchically organized programs with simpler neurocognitive functions trained prior to more complex functions, both rely heavily on task practice, and both carefully titrate task difficulty according to the participant's ability level. The primary hypothesis of the approach is that minimizing invocation of verbally mediated guidance and other superordinate executive cognitive mechanisms, and instead placing emphasis on implicit practice-related learning, will facilitate acquisition of elementary cognitive skills in schizophrenia. A corollary assumption is that any evident improvements in elementary cognition will extend to other key disorder features. NET uses Bracy's PSS CogRehab software (Bracy, 1995) coupled with a weekly group discussion for social information processing and has been merged with on-site hospital work therapy programs. Cognitive training consists of a series of exercises first focused on sustained attention, then divided and shifting attention, and then working and episodic memory as well as problem solving. Exercises are started at individually determined levels of difficulty at which each client is successful (e.g., 80% accuracy) to presumably engage underfunctioning brain systems and maintain high levels of positive reinforcement. Several large sample randomized controlled trials have shown that NET in combination with work therapy improves working memory, executive function, and affect recognition (Bell, Bryson, Greig, Corcoran, & Wexler, 2001); these effects generalize to improved work performance as measured by hours worked and wages earned (Bell, Zito, Greig, & Wexler, 2008).

The Brain Fitness program is composed of exercises that place a much greater emphasis on sensory processing than the Bracy exercises (Fisher, Holland, Merzenich, & Vinogradov, 2009); thus, it trains at a more elementary level of cognitive function. The first part of the training program is targeted at auditory

sensory processing and consists of practice in distinctions between frequency-modulated sound sweeps as the sweeps become faster and are separated by shorter and shorter intervals. Subsequent exercises train processing phonemes. The last set of exercises targets verbal and working memory and focuses on accurately identifying increasing lists of syllables in spatial and sequential contexts or listening to a series of verbal instructions and carrying them out. By improving the speed and accuracy of auditory information processing it is hypothesized that the mental representations that encoding and rehearsal processes operate upon will be strengthened, leading to improved cognitive function. Preliminary findings from this intervention were very strong. Fisher and colleagues (2009) reported large effect-size improvement in verbal episodic learning and memory (d = .86 and .89, respectively) in a sample of clients with schizophrenia randomly assigned to the Brain Fitness program. These effects persisted at a six-month follow-up (Fisher et al., 2010). More recent data from a multisite international randomized controlled trial (n = 55), however, while showing improvement on tasks trained in the Brain Fitness program, failed to find any effects of training on cognitive or functioning measures not directly trained in the protocol (Murthy et al., 2012).

Motivationally Focused Programs

Disruptions in motivation, which refers to the ability to initiate and sustain goal-directed activities, is a primary feature of schizophrenia that affects a broad array of dimensions of psychosocial function in the disorder and presumably plays a key role in the ability to persist and benefit from these highly effortful, comprehensive, and sustained programs of CR. The manualized Neuropsychological Education and Rehabilitation (NEAR) CR program developed by Medalia and her colleagues (Medalia, Revheim, & Herlands, 2009) places the emphasis of cognitive training on the motivational processes required for acquisition of cognitive skills. They hypothesize that the central stumbling block for acquisition of novel cognitive skills in schizophrenia involves deficits in motivation and volition that are both a central feature of the disorder and the consequence of repeated failure experiences secondary to cognitive and social impairments. Thus, by this view, for CR to have an impact on cognitive skills in schizophrenia, the intervention must be administered in a manner that enhances motivation. Features that improve motivation include client choice in CR exercises, multimodal exercises that are engaging and intrinsically rewarding, and contextualization for the client. The key factor for these exercises, according to the NEAR model, is that they promote independence and self-efficacy. NEAR is most often offered in groups of up to 10, in which clients meet two to three times per week in 45-minute sessions, working on computerized exercises at their own pace. While a range of different computerized interventions have been used in this approach, exercises are often "top down" in that they train a range of cognitive skills within the same task. As opposed to restorative programs, they do not place emphasis on sequential, hierarchical training of elementary neurocognitive function. For example, with respect to problem-solving training, these researchers have investigated the "Where in the USA is Carmen San Diego" software. Participants are asked to solve a crime through planning, organization, and inference based on clues offered by the program on how to identify and track a criminal. Participants travel around the United States conducting interviews to support a warrant for the suspect. The program simultaneously provides practice on problem-solving skills as well as more basic skills in attention, memory, and concentration.

In support of this approach, these researchers have manipulated personalization, choice, and contextualization in an experimental paradigm and found that these factors together influenced the degree to which people with schizophrenia acquired arithmetic skills from an arithmetic training task, as well as the extension of effects of this training to a measure of attention (Choi & Medalia, 2010). To date this approach has received additional empirical support from other type 1 randomized controlled trials, with evidence of improvement on neuropsychological measures distinct from those trained and durability in which treatment effects persist for four weeks after the cessation of treatment (Medalia, Revheim, & Casey, 2002a, 2002b).

Hybrid Programs

Cognitive Enhancement Therapy (CET), developed by Gerard Hogarty and his colleagues, is an intensive intervention that represents an admixture

of cognitive and social cognitive training exercises (see section below on social cognitive training). It consists of 75 hours of training in elementary attention function along with 56 group social cognitive treatment sessions focused on increasing mental stamina, promoting active rather than passive social information processing, and learning to abstract the superordinate emotional character of social relationships. Group exercises are focused on understanding social cues, including recognizing affect in others, making accurate attributions about mental states, and emotion regulation. Results from type 1 randomized controlled trials have revealed that the intervention produces improvements in composite neurocognitive measures and behavioral measures of social cognition, cognitive style, and social adjustment relative to an active, enriched supportive therapy condition. Larger effects of the intervention were evident after a second year of treatment, and effects of treatment on composite measure of cognition, along with cognitive style, social cognition, and adjustment, are durable at a year after cessation of treatment (Hogarty et al., 2004; Hogarty, Greenwald, & Eack, 2006).

Integrated Psychological Therapy (IPT), as developed and studied by Brenner, Roder and his colleagues in Europe (Roder, Mueller, Mueser, & Brenner, 2006), and Spaulding and his colleagues at the University of Nebraska (Spaulding, Reed, Sullivan, Richardson, & Weiler, 1999), integrates neurocognitive, social-cognitive, and psychosocial rehabilitation into a comprehensive psychosocial treatment program consisting of five modules for people with schizophrenia. (IPT targeted at schizophrenia shares no relationship to Interpersonal Therapy developed for depression [e.g., Stewart et al., 2014].) Cognitive differentiation, the first training module, is designed to remediate cognitive deficits in schizophrenia. The next two modules are targeted at cognition in a social context (social perception and verbal communication), and the last two are intended to train social skills (specifically, social skill and interpersonal problem solving). Training is conducted in 30- to 60-minute sessions, two or three times per week in groups of five to seven clients. Cognitive training in IPT is similar in certain respects to computer-assisted restorative interventions in that training is targeted at specific cognitive deficits that are impaired in schizophrenia; it differs from this approach because it takes place in a group interactive format. It also shares elements with CR strategy in that strategies are practiced for achieving goals and tasks used are more directly integrated into the acquisition of ecologically relevant behavior such as social skill, which is then trained directly at a different juncture in the treatment protocol. A meta-analysis including 29 studies of IPT showed that effect sizes for measures of neurocognition were in the moderate to large size (d = .61); importantly, effects were also evident, at a reduced magnitude, on measures of psychosocial functioning (d = .41).

Meta-Analyses of the Efficacy of Cognitive Remediation on Cognition, Function, and Symptoms

To facilitate comparisons of findings across different studies, this section of the chapter will present standardized estimates of effect-size impairment in samples of people with schizophrenia treated with CR versus those not treated with CR (Cohen's d) from peer-reviewed, published meta-analyses of CR treatment. For effect-size calculations, the mean score of one group (e.g., mean scores on an outcome measure at the end of an intervention period from a group of people with schizophrenia treated with CR) is subtracted from that of a second group (e.g., mean scores on an outcome measure at the end of an intervention period in people with schizophrenia not treated with CR). The participant-to-participant variability in scores within each condition on the outcome measure is quantified, pooled across groups, and included as part of the statistic. This permits research results across studies to be compared directly since the results of each study can be expressed in standardized units of separation, regardless of interstudy differences in the specific measure selected for that study and the range of values for that measure in a specific study. We use the commonly accepted metric of small, d = .2 to .4, medium d = .4 to .8, and large effect size (d > .8) change (Cohen, 1977). It is important to note that at an individual participant level, even a large effect size of .8 still indicates an overlap of 53% of individual scores between two populations; thus, scores on a specific measure will only differentiate people in the treatment condition slightly less than 50% of the time from people not in the treatment condition. While this might suggest poor discrimination, if a substantial (e.g., approximately 50%) proportion of people with schizophrenia improve on a specific measure of outcome after a new treatment in this research area, the

treatment would still be considered beneficial, assuming other indices of statistical significance are found and adverse effects of the new treatment are low.

To date seven quantitative meta-analyses of CR in schizophrenia have been published, with all but one (Pilling et al., 2002) supporting the efficacy of CR for improving cognitive outcomes targeted by these interventions (Fig. 7.2). More recent meta-analyses have also provided support for moderate effect size improvements in function after CR when compared to a control condition—but only when CR is paired with other psychosocial interventions. Modest effects on symptoms have also been reported.

McGurk and colleagues (2007) conducted the first large-scale meta-analysis in this research area; it consisted of 26 randomized, controlled studies of CR and 1,151 participants with schizophrenia. Results revealed that CR produced moderate-sized effects on cognitive outcomes (d = .41) and small effect size improvements in psychosocial (d = .36) outcomes and symptoms (d = .28). Despite marked differences in study sample and treatment characteristics, there was little evidence that duration of CR training, inpatient versus outpatient status, age, or other variables influenced observed cognitive outcomes. The effects of CR on function were considerably stronger when CR was paired with other rehabilitation interventions (d = .47 vs. d = .05).

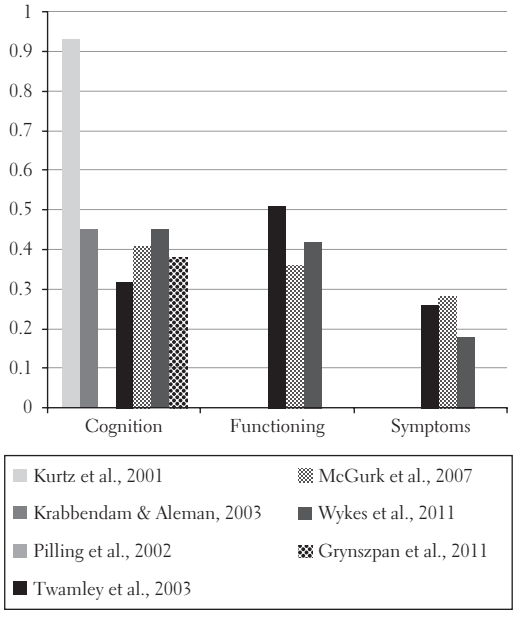

FIGURE 7.2 Effects of cognitive remediation on cognition, function, and symptoms in schizophrenia: results from effect size and formal meta-analyses.

These findings were confirmed in a more recent meta-analysis of 40 controlled studies of CR consisting of 2,104 participants (Wykes et al., 2011). Results revealed that CR produced moderate effect size improvement in cognitive outcomes (d = .45) and function (d = .42). This analysis was particularly important as it was the first to evaluate the impact of methodological rigor of CR studies on observed findings. Treatment factors such as duration, computer presentation, adjunctive psychiatric rehabilitation, and whether training was largely restorative or strategy-based were also evaluated. As in the study by McGurk and colleagues, effects on function were found to be larger when CR was administered as one element of a more general rehabilitation program, and there was some evidence for an advantage of strategy over restorative interventions on functioning, but not cognitive outcomes. There was also some evidence that having more symptoms leads to weaker treatment effect; however, even clients with high levels of symptoms showed some benefit. Other illness, demographic, and treatment factors did not influence treatment response, and the quality of the design methodology had no impact on observed treatment effects.

Predictors of Response to Cognitive Remediation

A small but growing number of studies have investigated the relationship of demographic features such as age, illness features such as positive and negative symptoms and amotivation, treatment characteristics such as duration and intensity of CR interventions, cognitive factors such as baseline level of cognitive skill at the start of CR treatment, and regional measures of brain volume from structural magnetic resonance imaging (MRI) to CR treatment response. In the first study of its kind, using 58 individuals with schizophrenia, Fiszdon and colleagues (2005) evaluated the relationship of demographics, symptoms, treatment, and neurocognition to the probability of showing normalized performance (improvement to within one standard deviation of healthy control performance) after CR training on a memory task that was an element of the comprehensive, computer-assisted, drill-and-practice remediation program selected by

the authors. The authors predicted that stronger sustained vigilance at study entry would predict normalized performance after the remediation intervention. As expected, results revealed that sustained visual vigilance, along with immediate verbal memory, time between termination of intervention and follow-up assessment, and clinical measures of hostility, accounted for 70% of the variance in normalization on the selected memory task.

Medalia and Richardson (2005) investigated the role of motivation, among other factors, in an analysis of three client databases in which CR "improvers" were distinguished from "non-improvers." They reported that motivation (as measured by voluntary participation in CR sessions), participant work style, and clinician experience were related to a positive response to NEAR CR treatment. Among neurocognitive measures, sustained attention was related to improvement across three samples of psychiatric inpatients and outpatients (these samples did not exclusively consist of people with schizophrenia). Participants were classified as "improved" if they improved on any proximal measure of neurocognitive function to a degree that could have occurred by chance only five times or less out of 100.

Kurtz and colleagues (2008) explored the relationship of four measures of neurocognitive function (crystallized verbal ability, auditory sustained attention and working memory, verbal learning and memory, and problem solving); two illness variables (total positive and negative symptoms); and the treatment variables of treatment intensity and duration to improvement on a measure of adaptive everyday life skills (UPSA) after a year of computer-assisted, restorative CR. CR was offered as part of intensive outpatient rehabilitation treatment that included exercise, case management, supportive group therapy, psychoeducation, and vocational counseling. Results of a linear regression model in 36 participants with schizophrenia revealed that auditory attention and working memory predicted a significant amount of improvements in performance-based measures of everyday life skills after CR, even when other neurocognitive variables in the model were accounted for.

Age was investigated as a moderating variable in studies of strategy-based CR in a pair of recent papers by Til Wykes and her colleagues (Kontis, Huddy, Reeder, Landau, & Wykes, 2013; Wykes et al., 2009). In both studies, participants were divided into younger (<40) and older (40 and up) samples. Wykes and colleagues (2009) evaluated a sample of 85 participants with schizophrenia in a randomized controlled trial, with memory, cognitive flexibility, and planning as primary cognitive outcomes and symptoms and self-esteem as secondary outcomes. The authors reported evidence of greater improvement in planning and cognitive flexibility in the younger group, along with improvements in negative symptoms. The follow-up study by Kontis and colleagues (2013) of 134 individuals with schizophrenia pooled across two studies revealed that when cognitive reserve estimates, as measured by premorbid IQ and vocabulary, were taken into account in addition to age, age remained a significant predictor of treatment response: Participants under 40 showed improvement in working memory after CR while those 40 and older failed to show a significant response. Proxy measures of cognitive reserve only predicted the likelihood of showing practice effects on the working memory outcome measure in younger participants regardless of treatment condition (CR or control).

In a particularly novel study employing structural neuroimaging indices, Keshavan and colleagues (2011) investigated the relationship of gray matter volume and cortical surface area to treatment outcome in 50 people with schizophrenia randomly assigned to a hybrid CR program, CET, or enriched supportive therapy. The authors hypothesized that greater pretreatment cortical volumes in key illness-linked brain regions (labeled by the authors as "brain reserve"), specifically in the frontal and temporal lobes, would predict cognitive/social cognitive outcomes over a two-year period in individuals in an early phase of illness. Results revealed that gray matter volumes and surface areas at baseline were linked to improved social cognitive task performance, but not cognitive task performance, at a one-year assessment. Both groups were similar in the magnitude of their treatment response to CET by the second year of treatment. Importantly, all relationships were specific, with structural neuroimaging measures predicting response to the active intervention when compared directly to the predictive value of these measurements for change in the control training condition.

In summary, age (under 40), sustained attention and memory, clinical ratings of hostility, therapist training, and client motivation and work style have all been linked to a positive response to CR. Two key limitations of this literature limit firm conclusions. First, programs of CR in these studies have varied widely;

for example, predictors of response to stand-alone restorative CR training may be quite different from predictors of response to hybrid programs consisting of CR and other treatment elements such as social cognitive training and social skills training. Second, only two studies in this section explicitly compared predictors of response to CR to a control condition, so the specificity of these predictor variables to CR response remains largely unknown. These findings do suggest that modifications of existing CR programs will likely be necessary to address the needs of clients with particularly low motivation for treatment, poor cognitive function, and older age. Indeed, with respect to motivation, recent research suggests that intrinsic motivational levels remain a significant stumbling block to CR participation and directly predict CR learning outcomes, and these effects are larger than those seen for more extrinsically motivated psychosocial interventions for schizophrenia (e.g., supported employment programs; Medalia & Saperstein, 2011). The good news is that intrinsic motivational levels in schizophrenia are dynamic rather than static and can be manipulated by increasing a sense of agency and self-efficacy in the context of CR and contextualizing learning by making the goals of CR more personally relevant (Choi & Medalia, 2010).

Cognitive Remediation + Adjunctive Pharmacotherapy

In a novel research avenue with considerable promise, two randomized controlled trials during the past 2 years have combined adjunctive medications designed to enhance neural plasticity with CR procedures. In both reports, an *N*-methyl-D-aspartate receptor (NMDAR) agonist or enhancer was used to promote neural plasticity in the context of CR. The rationale for the approach is that medications that enhance neural plasticity may have little effect on measures of neurocognition if they are administered in isolation to people with schizophrenia in the context of impoverished social environments with little cognitive stimulation. Only when cognitive functions are stimulated through repeated practice may the effects of enhanced neural plasticity be capitalized upon. In both studies the medications affecting the NMDAR system were selected for two reasons: (1) the clear role of the NMDARs in promoting neural mechanisms of plasticity that have been associated with long-term memory and fear extinction and (2) the hypothesized role of NMDAR dysfunction in the genesis of the disorder. Studies have shown evidence of NMDAR dysfunction in schizophrenia and the simulation of many key symptomatic features of schizophrenia in healthy participants following NMDAR blockade (e.g., Krystal & Moghaddam, 2011).

In the largest sample study to date, D'Souza and colleagues (2013) conducted a blinded, randomized, placebo-controlled type 1 study of 104 people with schizophrenia at two sites in the United States and India. Participants were assigned to one of four groups: (1) CR plus the NMDAR agonist d-serine, (2) CR plus placebo, (3) control CR plus d-serine, and (4) control CR plus placebo. CR consisted of 20 computer-assisted, restorative training tasks targeted at attention, memory, verbal and visuospatial working memory, and executive function. It was administered for five hours a week in two or three weekly sessions over 12 weeks. Participants were assessed with a battery of neurocognitive instruments at baseline, at the end of the trial, and at a 24-week follow-up. Results revealed that a sustained intervention consisting of combined pharmacotherapy and CR is feasible and well tolerated by individuals with schizophrenia, with completion rates of the 12-week trial over 80%. Consistent with previous research, results revealed effects of the CR intervention on verbal working memory, but no evidence of d-serine enhancement effects on primary indices of cognition and function. The authors concluded that overly low dosages of d-serine along with limited trial power and inflated placebo effects associated with this type of trial design may have limited detection of the effects of the combined treatment.

In a related study, Cain and colleagues (2014) investigated the effects of an eight-week CR intervention offered in combination with d-cycloserine, another NMDAR agonist with more specific effects on a subgroup of NMDAR receptors that include an NR2C subunit (relative to other NMDAR agonists such as d-serine). NMDAR receptors that include the NR2C subunit are thought to be particularly crucial for facilitating the neural plasticity associated with fear learning in animal models and to show reduced expression in the prefrontal cortex of people with schizophrenia (Krystal & Moghaddam, 2011). Forty chronic outpatients with schizophrenia treated with antipsychotic medications were randomly assigned to one of two conditions: once-weekly d-cycloserine

plus CR or placebo plus CR. CR consisted of either three- or five-times-per-week restorative CR based on participant choice (Brain Fitness, PositScience, San Francisco, CA). Outcome measures included an auditory discrimination task that was trained in CR, standardized neurocognitive measures (MATRICS battery) that were not trained directly in the CR program to assess the breadth of effects, and symptom and functioning measures. Completion rates for the trial were over 85%. Results revealed that d-cycloserine facilitated performance on the auditory discrimination task trained as one of the key elements of the CR program, but that participants assigned to the placebo group showed improved performance on an overall index of neurocognition from the neurocognitive test battery. The latter finding suggests that d-cycloserine may have in fact attenuated the effects of CR on nontrained neurocognitive measures in this study. The authors concluded that d-cycloserine may serve to enhance specific neuroplasticity for the acquisition of a trained task but may not enhance or may even interfere with CR effects more generally on untrained cognitive tasks. Taken together, these findings suggest that lengthy, combined CR and adjunctive pharmacotherapy treatment trials are feasible and well tolerated by people with schizophrenia. Results to date using NMDAR agonists have been negative with respect to enhancement of restorative CR effects on cognitive outcomes not directly trained in the CR program, with some evidence of enhancement of performance on trained tasks. The number of studies to date has obviously been small, and the results provide a rationale for additional, more highly powered treatment trials with perhaps other pharmacological agents designed to promote neural plasticity and facilitate CR effects.

SOCIAL COGNITIVE TRAINING

Social Cognition in Schizophrenia

Social cognition is defined as those cognitive processes necessary for the perception, interpretation, and processing of social stimuli (Fiske & Taylor, 1991). Social cognition is typically conceived as a complex set of cognitive operations that are built upon elementary skills in neurocognition discussed in the previous section of this chapter, but are not solely defined by these skills. For example, an employer may have a Superior level IQ score and outstanding attention and memory skills but still fare quite poorly when negotiating a delicate interaction with a supervisee regarding the supervisee's work product if the employer's social cognitive skills are underdeveloped. In contrast, a person with borderline IQ, along with attendant impairments in attention, memory, and problem solving, is likely to have a difficult time negotiating social situations without the requisite skills in attending to and remembering facial expression, voice prosody, and other paralinguistic expressions.

Social cognition is distinguished from nonsocial cognition on the basis of the following:

1. The content of information that is operated on—namely, socially relevant stimuli that are usually personally relevant, that are often affectively charged, and that focus on either perceptions of individuals in the social environment or the steps involved in negotiating complex social situations;
2. The products of social cognitive processes, which are focused on inferring traits or dispositions in others, rather than on a computational outcome;
3. Less emphasis placed on performance deficits as compared to healthy controls; instead there may be differences in biases in the way social information is processed in clinical populations as compared to healthy controls; and
4. Social stimuli are typically not static but reflexive, influencing the perceptions of the perceiver (Penn, Corrigan, Bentall, Racenstein, & Newman, 1997).

Over the past 10 years there has been increasing focus on component skills that make up social cognition in schizophrenia. A consensus statement by a group of experts on social cognition convened by the National Institute of Mental Health (Green, Olivier, Crawley, Penn, & Silverstein, 2005) identified five key areas of social cognition: *Theory-of-Mind (ToM)*, or the ability to infer another's perspective or mental state based on his or her speech and behavior; *social perception*, or the ability to decode environmental cues regarding the appropriate application of social rules and roles; *social knowledge*, which refers to the possession of knowledge regarding appropriate social rules and roles that govern social interaction; *attributional bias*, which reflects a style of attribution that focuses on the source of positive

or negative social events relating to internal (self), external (other), or situational factors; and *emotional processing*, the ability to understand and manage emotion as perceived in others or in oneself through a variety of behavioral and verbal cues. A recent meta-analysis of 112 studies of social cognition in schizophrenia that included nearly 4,000 individuals with schizophrenia and 3,500 matched controls showed that people with schizophrenia experienced large effect size impairments on skills in social perception (g = 1.04), ToM (.96), and emotion perception (g = .89) and processing (g = .88; Savla, Vella, Armstrong, Penn, & Twamley, 2013). Thus, deficits in social cognition in schizophrenia are substantial and widespread across a variety of component social cognitive processes.

Social Cognitive Deficits and Functional Status in Schizophrenia

Over the past 10 years a growing number of studies have investigated the relationship of a variety of domains of social cognition to a variety of indices of functional measures in schizophrenia. One conceptual model linking social cognitive deficits to a variety of measures of outcome has been delineated by Penn and his colleagues (Penn, Sanna, & Roberts, 2008). According to their view, when skills in emotion and social perception are disrupted, misperceptions of facial affect and other nonverbal cues result, leading a person with social cognitive deficits or nonadaptive information processing biases to misinterpret, for example, anxiety for anger in a coworker. Systematic biases in attribution in turn lead people with social cognitive impairment to assume that the anger is directed toward themselves, leading to reciprocal anger targeted at the coworker. The coworker then withdraws from social interactions based on this expression of anger. In turn, anger in the person with social cognitive impairment disrupts ongoing activity in his or her work life and decreases subjective quality of life. In this way, disruptions in elementary social cognitive processing can cascade, creating a variety of downstream effects on different indices of psychosocial function.

Conclusions from synthetic reviews of relationships between social cognition and functioning (e.g., Couture, Penn, & Roberts, 2006) provide support for this conceptual model, suggesting numerous and replicated links between specific aspects of social cognitive skill and different aspects of functional status. Results from one review of 23 largely cross-sectional studies that investigated four domains of social cognitive skill (social perception, emotion perception, ToM, and attributional style) and four measures of functional status (social behavior within a treatment milieu, community functioning, social skill, and social problem solving [the ability to generate solutions to everyday social problems]) revealed a consistent relationship between social perception and social problem solving, community functioning, and behavior in the milieu. Emotion perception had a consistent albeit modest relationship with community function, social skills, and social behavior in the milieu. Results also revealed a link between ToM and social skills. More recent work has confirmed these findings longitudinally by showing that social cognitive deficits in emotion processing, ToM, and social perception in a first episode of schizophrenia predicted work function at a 1-year follow-up after controlling for differences in work function explained by symptoms (Horan et al., 2012).

Other reviews (Schmidt, Mueller, & Roder, 2011) have suggested that impairments in social cognition in schizophrenia may in fact mediate the relationship between elementary neurocognitive function and psychosocial functioning. That is, neurocognition may exert its effect on psychosocial function by affecting social cognitive skills negatively; this in turn diminishes psychosocial function. This is important in that it might suggest that interventions targeting social cognitive skills directly could have a greater impact on functioning than those targeting neurocognition, since they are influencing skills more proximal to the disability itself. In a review of 15 studies of the role of social cognition as a mediator of the effects of neurocognition on function, 14 of these studies showed that, despite wide differences in indices of social cognition and neurocognition and a range of functioning measures, including social behavior in the milieu, community function, social problem solving, and social skills, there was a mean, standardized indirect effect size of .20 for social cognitive measures as mediators of the effects of neurocognitive skills on function.

Methods of Social Cognitive Training in Schizophrenia

Evidence of replicated links between skills and information processing biases in domains of social

cognitive function and aspects of psychosocial status, along with the mediating effects of social cognition on the relationship between neurocognition and function, give currency to the idea that social cognitive skills may be a crucial function to target for novel therapies for improving functional outcome in schizophrenia. As can be seen in Figure 7.3, while still in an inchoate stage of research, there have been a growing number of controlled studies investigating the effectiveness of social cognitive training (SCT) interventions, with a quadrupling of the cumulative number of published studies over the past eight years.

SCT programs have typically been considered "targeted" or "broad-based." Targeted programs treat one dimension of social cognitive deficits (e.g., facial affect recognition), whereas broad-based interventions treat several dimensions of social cognition in the same intervention or treat one or more areas of social cognition as well as other dimensions of the disorder such as cognitive or social skill deficits. Programs are best conceptualized along a continuum rather than rigidly categorized as one approach or the other; for example, an SCT program targeting two dimensions of social cognition would be somewhere toward the middle of this continuum. While social cognitive processes include biases in information processing as well as performance deficits, to date most programs have focused on remediation strategies for performance that are analogous to those in CR, including drill-and-practice and strategy training to enhance performance in areas of social cognition; debiasing strategies have been much less frequently employed.

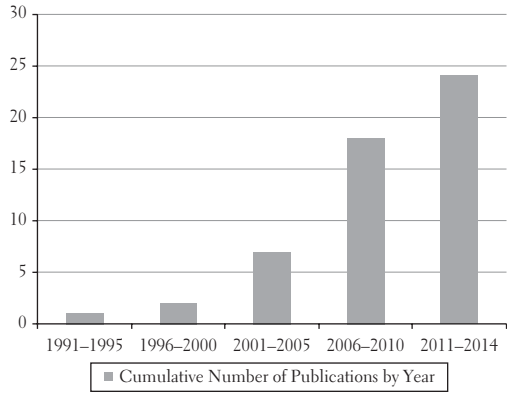

FIGURE 7.3 Cumulative number of controlled studies on social cognitive interventions in schizophrenia.

Targeted Programs

To date, targeted SCT programs have addressed two major areas of social cognitive deficit: ToM and facial affect recognition. In a pilot study ($n = 14$) Kayser and colleagues (2006) investigated the use of verbalization strategies in which individuals with chronic schizophrenia provided descriptions of 12 20- to 70-second scenes from French cinema. If descriptions were not offered spontaneously, therapists prompted participants to describe what they had seen in the film. If participants made attributions regarding the mental/emotional state of characters, participants were asked how they came to their conclusions. If they offered only concrete details of the scene and failed to mention the characters' intentions, participants were prompted by the therapist to describe the characters' mental/emotional state. Results revealed improvement on a nonverbal ToM outcome task that used stimuli that were distinct from the training videos (the Intentions Inference Task) in the verbalization group but not in the nonverbalization treated control group.

With respect to affect recognition training, early studies investigating the effects of reinforcement in the form of monetary compensation for correct performance and facial mimicry of emotional faces revealed that both interventions improved facial affect recognition immediately after the intervention, but effects were not durable at a one-week follow-up (Penn & Combs, 2000). Subsequent interventions have targeted facial affect recognition deficits through attentional shaping, in which visual scan paths in individuals with schizophrenia are modified through the use of attentional prompts (the brief presentation of a large cross on the screen) that focuses the attention of the participant on the eyes and mouth of the face, areas likely to provide the most information regarding the affective valence of a face (Combs et al., 2008). Other studies have investigated the use of didactic instruction on differentiating emotions that may appear to be overlapping, with corrective feedback and repetition to improve identification of briefly presented "microexpressions" (15-ms "flashes" of facial affect). These effects are substantial, enhancing performance to that of healthy controls, and are beyond those associated with passive exposure to faces expressing affect (Russell, Green, Simpson, & Coltheart, 2008). More sustained 12-session training programs in affect recognition have also been employed with improvements in affect recognition

skills that are specific and evident relative to active control conditions (Wolwer et al. 2005).

Taken together, targeted studies of SCT show that difficulties in two aspects of social cognitive skills (ToM and facial affect recognition) are modifiable with brief interventions that target impairments directly. These interventions have varied widely in method from simple task practice and corrective feedback to didactic instruction, verbalization, mimicry, and motivational enhancement through monetary reinforcement of correct responses.

Broad-Based Programs

In recent years, an exciting development in SCT programs has been the formulation and initial assessment of two broad-based, sustained training programs that comprehensively target a broad array of social cognitive skills in schizophrenia: Social Cognition and Interaction Training (SCIT), developed by David Penn and his colleagues at the University of North Carolina-Chapel Hill, and a novel integrated social cognitive training program derived partially from SCIT called Social Cognitive Skills Training (SCST), developed by William Horan and his colleagues at UCLA.

SCIT is a 20-week group intervention that includes three interrelated modules. Module One is devoted to emotion recognition using practice-based remediation, didactic instruction, verbalization skills, and corrective feedback and includes specific training in identifying and managing paranoid feelings. A second module, targeting ToM and attributional style, is aimed at making clients better social detectives, providing practice in questioning assumptions, generating alternative hypotheses regarding others' thoughts and feelings, distinguishing facts from assumptions in drawing conclusions about social situations, and acquiring the social skills to ask questions and gather additional information before making assumptions about the source of other people's behavior. In the last module, skills in applying techniques in the first two phases of the program to everyday life situations are taught and practiced. Initial findings from non-randomized type 2 designs have been promising, showing evidence that the program elevates skills in social cognition relative to control conditions (e.g., Roberts & Penn, 2009). The first type 1 randomized controlled trial of the intervention was conducted in the United States and has been published. It included 66 people with chronic schizophrenia and revealed that individuals treated with SCIT showed improved social functioning, negative symptoms, and hostile attributional bias relative to a treatment-as-usual control group, with evidence that clients attending more treatment sessions showed greater benefit. Thus, SCIT produced generalized improvements in the treated group. Somewhat surprisingly, there were only small, non-significant effects of SCIT on measures of affect recognition and ToM treated directly in this study (Roberts et al., 2014).

A recent type 1 randomized controlled trial of the related treatment program SCST has shown efficacy as well, with improvements in facial affect recognition and emotion perception, but not symptoms or neurocognition, in SCST-treated participants relative to active control groups treated with neurocognitive remediation or illness management training (Horan et al., 2009, 2011).

Meta-analysis of Effects of Social Cognition Training on Social Cognition, Function, and Symptoms in Schizophrenia

As shown in Figure 7.4, a recent meta-analysis of 19 studies of SCT (Kurtz & Richardson, 2012) revealed preliminary support for the efficacy of these interventions for improving social cognitive function, psychosocial functioning and some aspects of psychiatric symptoms. The meta-analysis included both targeted and broad-based programs of SCT. With respect to social cognitive measures, the meta-analysis revealed reliable, moderate and statistically significant effect size improvements in facial affect recognition (d = .71; 14 studies) and ToM (d = .46; 7 studies), relative to a control condition. Further, preliminary evidence of generalization with improvement on measures of total symptoms (d = .68; 7 studies) and psychosocial function (d = .78; 6 studies) was observed. Indeed, moderate-sized effects of these interventions on these more distal outcome measures were particularly noteworthy since they were similar in magnitude to those of social cognitive measures directly trained in these interventions. This finding suggests a close relationship between improvements in social cognitive skill and a variety of indices of functional outcome and generalized symptoms. Effects of these interventions on measures of social

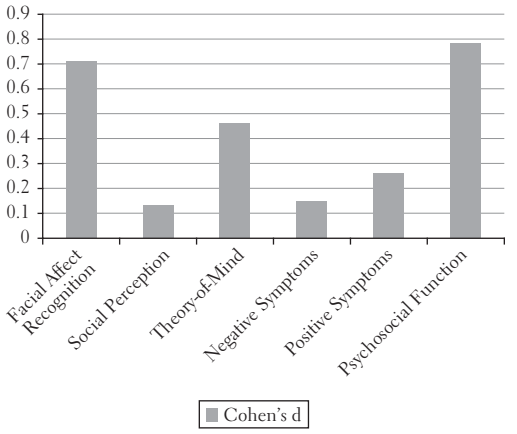

FIGURE 7.4 Meta-analysis of effects of social cognitive training on social cognitive, symptom, and function measures in schizophrenia from nineteen controlled studies.

Adapted from: Kurtz, M. M., & Richardson, C. L. (2012). Social cognitive training for schizophrenia: A meta-analytic investigation of controlled research. *Schizophrenia Bulletin*, 38, 1092–1104.

perception and positive and negative symptoms were nonsignificant. These latter findings suggest that these training programs improve more generalized symptoms of anxiety and depression rather than symptoms that are more closely linked to the diagnosis of schizophrenia, including delusions, hallucinations, and social withdrawal. There was no evidence from the meta-analysis of effects of social cognitive training effects on measures of attributional bias. At the time of the analysis, however, only four studies had investigated the effects of these training programs on this index of social cognition. Moderator analyses revealed that clients with a longer duration of illness were more likely to benefit on measures of facial affect recognition and ToM, and younger, more medicated samples showed more general effects of SCT on measures of function and general symptoms.

CONCLUSIONS AND FUTURE RESEARCH

A wide range of cognitive interventions have been developed to address persistent deficits in neurocognition and social cognitive functioning in schizophrenia. These deficits are thought to impair successful psychosocial functioning and to be resistant to pharmacotherapy of schizophrenia. With respect to cognitive training programs, these methods differ in terms of whether they (1) teach strategies that work around cognitive deficits, (2) undertake restorative, drill-and-practice training, (3) maximize motivational set, or (4) represent hybrid programs that consist of cognitive training procedures with accompanying training in more molar social cognitive and social skills. Results from meta-analyses consisting of many type 1 research studies have revealed (1) strong support for moderate (d = .46; Wykes et al., 2011) improvements on measures of neurocognitive function distinct from the tasks trained as part of specific remediation protocols and (2) generalization of these effects to function (d = .42; Wykes et al., 2011) when offered along with other evidence-based psychosocial treatment programs. These findings suggest that these training interventions produce improvement in the underlying neurocognitive skills necessary to complete neurocognitive tasks, rather than simply teaching skills to the specific test. Even more importantly, these findings indicate that these improvements in cognition generalize to broader psychosocial function by boosting the effects of psychosocial interventions targeted at key areas of functioning in schizophrenia. A corollary to this conclusion is that there is little evidence that stand-alone CR programs enhance functioning. Taken together, these findings are remarkable given the wide differences in sample composition, method of remediation, type of adjunctive psychosocial treatment, and duration and intensity of intervention administration in studies in this research area.

However, there are several areas of concern that the CR field needs to address to be accepted as a front-line, evidence-based practice. First, the multitude of different strategies that have been used to intervene with cognitive deficits makes it unclear which interventions are most effective. These differences in methods in the CR literature have been identified by opinion leaders in the field as a crucial limitation of this treatment research area. In fact, the most recent Patient Outcomes Research Team (PORT) psychosocial treatment recommendations, commissioned by the U.S. Department of Health and Human Services, concluded that "while the literature to date provides a foundation for further research, more work is needed before a concrete recommendation for cognitive remediation can be offered to the field. There are…principal considerations underlying this conclusion…that the variation among

cognitive remediation models and programs is too great to allow identification of key elements of the intervention" (Dixon et al., 2010, p. 60).

Second, while there has been substantial growth in research over the past decade, a continued limitation in the field is the still-small number of CR studies assessing the generalization of cognitive training effects to functional outcome measures distal from the remediation intervention. In the meta-analysis by Wykes and colleagues (2011), 18 studies included functional outcome measures. These measures varied widely in terms of whether they were clinician-rated, performance-based (based on a laboratory assessment of life or social skills), or global ratings of function. It seems highly unlikely that CR interventions would produce equivalent effects on such diverse outcome measures bearing such different relationships to neurocognitive functioning. To improve our understanding of the mechanisms of action of remediation interventions, future studies will benefit from the use of a set of outcome measures that vary systematically in terms of their proximity to the locus of the remediation intervention. Furthermore, the specific relationship and any "threshold effects" between improvements on specific CR training tasks and improvements on cognitive outcome measures distinct from these training tasks, and in turn the relationship of improvement in these measures to improvements in functioning, is understudied and remains largely unknown. This absence has served as an impediment to the field. One recent report has tied CR-related improvements in neurocognitive function (planning skills) directly to improvements in work quality related to a work therapy program, but effects were modest (Wykes et al., 2012). Further study of these relationships will be crucial for the field to move forward in understanding the mechanisms of CR effects as well as how to maximize these effects.

Third, amotivation, a central feature of schizophrenia since its definition at the turn of the 20th-century, influences the ability of all clients to benefit equally from these time- and effort-intensive interventions. Levels of intrinsic motivation play a large role in client outcomes in CR and likely explain why some estimates suggest that as many as 40% to 69% of people who participate in CR interventions are "non-responders" (Medalia & Richardson, 2005). Findings that motivational states are mutable in schizophrenia (Medalia & Saperstein, 2011) suggest an important future direction for increasing the accessibility of these CR programs.

Fourth, self-reported life satisfaction and self-esteem, constructs that are central to any concept of client recovery from severe mental illness, have been evaluated only rarely as treatment endpoints. Accordingly, the relationship between these measures and changes in performance-based and clinician-rated measures of functional status after rehabilitation interventions remains unclear and even paradoxical in some studies (Brekke, Kohrt, & Green, 2001; Edmondson, Pawha, Lee, Ho, & Brekke, 2012). Indeed, improvement in cognitive functions may facilitate upward social comparisons, which lead to a consequently diminished sense of competence in adaptive everyday function and social relations. Thus, the effects of CR on self-reported quality of life remain largely unknown, do not clearly co-vary with improvements in objective psychosocial function, and should be an important focus of future study.

Fifth, at least one report has suggested a role of clinician training in the likelihood of response to CR interventions (Medalia & Richardson, 2005), but the question is largely understudied. Thus, the role of training in disseminating this family of interventions to clinical practice remains unclear. Training requirements are likely to differ based on approach. Computer-assisted restorative approaches, for example, are likely to require a much lower level of clinician training than the one-on-one training that is characteristic of many strategy-based programs (e.g., CRT).

Compared with cognitive treatments, the development and careful empirical validation of SCT programs are in a much earlier state of development, although interest and corresponding efforts are intensifying rapidly in light of the key role of social cognition in a variety of domains of psychosocial function. A growing number of targeted social cognitive interventions, including many type 1 studies, has revealed strong support for the idea that deficits are modifiable and that improvements in the key social cognitive domains of affect recognition and ToM can be attained with very brief motivational, attentional, didactic, and self-verbalization strategies. Importantly, in some cases these effects are durable. While SCT has been a key element of several validated, multimodal treatment programs consisting of CR, social skills training, and other interventions (e.g., Roder et al., 2006), for the first time two

sustained, comprehensive, stand-alone SCT packages have been developed (SCIT and SCT). Both have shown promise for improving social cognition in four type 1 and several type 2 studies. Studies to date, however, are small in number and have been largely preliminary and focused on development and feasibility. Thus, the ultimate value of these treatments will depend on the results of larger, ongoing and future, well-powered treatment trials.

In conclusion, CR and SCT have rapidly gained an evidentiary basis that suggests they will be key elements of the next generation of empirically supported treatments for schizophrenia. In light of the specificity of treatment effects to date, with generalization elusive in the absence of multimodal treatments, efforts geared toward understanding methods of integration of CR and SCT with other psychosocial and neuroscience-based pharmacological treatments represent the next frontier for enhancing recovery processes in schizophrenia. Indeed, these novel treatments, along with methods of cognitive-behavioral therapy tuned to the treatment of psychosis, and well-supported treatment mainstays such as social skills training, supported employment, and family interventions, all serve as an increasingly large bulwark against the therapeutic nihilism that has pervaded the application of psychological treatments over the past century for this highly underserved and still ill-understood population.

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8

Pharmacological Treatments for Bipolar Disorder

Paul E. Keck Jr.
Susan L. McElroy

The vast majority of clinical trials in patients with bipolar disorders have been conducted in groups with bipolar I illness, although a few trials have recently emerged specifically in patients with bipolar II disorder. The pharmacological management of bipolar disorder involves the treatment of acute manic, hypomanic, mixed, and depressive episodes, as well as the prevention of further episodes and subsyndromal symptoms. Lithium, divalproex, carbamazepine, haloperidol, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and asenapine have demonstrated efficacy in the treatment of acute mania in randomized controlled (type 1) trials. Although the pharmacological treatment of acute bipolar depression remains understudied, data from randomized controlled trials indicate that lithium, olanzapine, olanzapine–fluoxetine, quetiapine, lurasidone, tricyclics, monoamine oxidase inhibitors (MAOIs), and fluoxetine have efficacy in this phase of the illness. The optimal duration of antidepressant treatment, in combination with mood stabilizers, is still unknown. Lithium, lamotrigine, olanzapine, aripiprazole, quetiapine, and risperidone (long-acting, injectable) have been shown to have efficacy in relapse prevention. Less extensive data suggest that divalproex and carbamazepine are also efficacious as preventive treatments.

INTRODUCTION

Bipolar disorder is a common, severe, and recurrent psychiatric illness. In the United States, the 12-month prevalence rate of bipolar I and II disorders is estimated at 2.6% (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). In 1990, bipolar disorder was the sixth leading cause of disability worldwide and was projected to remain so in the first two decades of this century (Murray & Lopez, 1996). Bipolar disorder is characterized by disturbances in mood, cognition, and behavior and is often associated with psychotic symptoms (McElroy, Keck, & Strakowski, 1996b). Untreated bipolar disorder carries substantial risks of morbidity and mortality (Mitchell, Slade, & Andrews, 2004). Morbidity is not simply limited to mood episodes themselves; for example, full recovery of functioning often lags behind remission of symptoms by many months (Dion, Tohen, Anthony, & Waternaux, 1988; Keck et al., 1998). In addition, recurrent mood episodes may lead to progressive deterioration in functioning between episodes, and the number of episodes, in turn, may adversely affect subsequent treatment response and prognosis (Prien & Gelenberg, 1989; Swann, Bowden, Calabrese, Dilsaver, & Morris, 1999). Thus, morbidity due to the illness is not limited to acute mood episodes but may linger and lead to prolonged deficits in social and vocational functioning (Calabrese et al., 2003b; Fagiolini et al., 2005). Bipolar disorder can also be a

lethal illness: Suicide attempts are made by at least 25% of patients (Hopkins & Gelenberg, 1994).

Bipolar disorder is a highly heritable illness (Gershon, 1989). Concordance rates between monozygotic twins for bipolar disorder range from 65% to 75% compared with concordance rates for dizygotic twins of approximately 14% (Gurling, 1995). In family studies, the lifetime prevalence rates of mood disorders among first-degree relatives of bipolar probands are elevated compared with prevalence rates for these disorders in first-degree relatives of people without psychiatric illness (Gurling, 1995).

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM*-5; American Psychiatric Association [APA], 2013) delineates seven classifications of bipolar disorder: bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder. There are several changes from *DSM-IV* (APA, 1987) in the bipolar disorder section. Bipolar disorder not otherwise specified is eliminated as a diagnosis. Moreover, bipolar and related disorders are separated nosologically for the first time from depressive disorders, and positioned between "schizophrenia spectrum and other psychotic disorders and depressive disorders in recognition of their place as a bridge between the two diagnostic classes in terms of symptomology, family history, and genetics" (APA, 2013, pp. 123). As in *DSM-IV*, the *DSM-5* criteria for manic, hypomanic, and depressive episodes are summarized in *DSM*-5. Mixed episodes have been replaced by the specifier "with mixed features" (APA, 2013, pp. 127). The criteria for bipolar I disorder require the presence of at least one manic episode; the manic or depressive episode is not better accounted for by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder. The criteria for bipolar II disorder require at least one hypomanic episode and one or more current or past major depressive episodes. The criteria for cyclothymic disorder require, for at least 2 years (in children and adolescents for at least 1 year), the presence of numerous periods of hypomanic and depressive symptoms that do not meet respective criteria for hypomanic or depressive episodes; the person has not been without hypomanic or depressive symptoms for more than 2 months at a time and the hypomanic and depressive symptoms have been present for at least half the time; and no major depressive, manic, or hypomanic episode has been present; the symptoms in Criterion A are not better explained by a schizophrenia spectrum disorder, are not attributable to the physiological effects of substances or another medical condition, and the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Recent studies suggest that the duration criterion for hypomania of 4 days is arbitrary and longer than many patients with bipolar II disorder experience hypomanic symptoms (Benazzi & Akiskal, 2003).

The vast majority of psychopharmacological treatment research has focused on patients with bipolar I disorder. Thus, this chapter will review, primarily, the treatment of bipolar I disorder. The few studies that included patients with bipolar II disorder will be noted as such. Since the pharmacological treatment of bipolar I disorder involves the acute treatment of manic, mixed, and depressive episodes, as well as maintenance treatment to prevent cycling, recurrent mood episodes, and subsyndromal symptoms, we review below studies of both acute and long-term treatment. Finally, because studies of the pharmacological treatment of bipolar disorder vary in design, we will make careful distinction between conclusions based on randomized controlled trials and open trials, case series, and case reports.

PSYCHOPHARMACOLOGICAL TREATMENT FOR ACUTE MANIC AND MIXED EPISODES

Lithium

In 1970, lithium was the first drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of "manic episodes of manic-depressive illness" (Goodwin & Jamison, 1990). Six controlled studies demonstrated that lithium was superior to placebo for the treatment of acute mania (Bowden et al., 1994, 2005; Goodwin, Murphy, & Bunney, 1969; Maggs, 1963; Schou, Juel-Nielson, Stromgren, & Voldby, 1954; Stokes, Shamoian, Stoll, & Patton, 1971). Early lithium trials had several methodological limitations that were addressed in more recent

studies. For example, only two studies (Bowden et al., 1994, 2005) used a parallel design, whereas the earliest four studies were crossover trials of varying duration (Goodwin et al., 1969; Maggs, 1963; Schou et al., 1954; Stokes et al., 1971). Two studies used nonrandom assignment to lithium or placebo (Goodwin et al., 1969; Stokes et al., 1971), and the diagnostic criteria used to define bipolar disorder in the early lithium studies (Goodwin et al., 1969; Maggs, 1963; Schou et al., 1954; Stokes et al., 1971) were not necessarily comparable to those of the *DSM-IV* (APA, 1987) or *DSM-5* (APA, 2013).

In the first placebo-controlled, crossover study, Schou and colleagues. (1954) reported a definite response in 12 (40%) and a probable response in 15 (50%) of 30 patients with typical bipolar disorder based on a global impression of improvement. In the first study to use formal rating scales and to analyze data statistically, 28 patients with mania were randomized to three consecutive 14-day periods of lithium-rest- placebo or placebo-rest-lithium (Maggs, 1963). Results were based only on the 18 study completers. In this group, lithium was superior to placebo during the second week of treatment.

In the first United States study, Goodwin and colleagues (1969) compared the longitudinal efficacy of lithium with placebo in 12 patients with mania; 8 (67%) displayed a complete response and 1 (8%) a partial response to lithium. Stokes and colleagues (1971) used a crossover design with alternating 7- to 10-day trial periods on lithium or placebo. These brief trial periods may have limited the opportunity for patients to display a more substantial lithium response, while the equally brief placebo period may have been confounded by residual lithium effects. With these caveats, Stokes and colleagues (1971) reported a 75% response rate (partial or full) with lithium, compared with 40% on placebo.

Two more recent studies used lithium as an active comparator in placebo-controlled, parallel-group trials of divalproex (Bowden et al., 1994) and quetiapine (Bowden et al., 2005). In both trials the mean improvement in lithium-treated patients at study endpoint was superior to placebo and comparable to the investigational agent. Response rates among active treatment groups were also comparable after 3 weeks (divalproex 48% lithium 49%, Bowden et al., 1994; quetiapine 53%, lithium 53%, Bowden et al., 2005). Significant differences in improvement in manic symptoms were evident in patients receiving lithium or divalproex compared with placebo at day 10 (Bowden et al., 1994), and in patients receiving lithium or quetiapine compared with placebo at day 7 (Bowden et al., 2005). Several post hoc analyses have attempted to identify predictors of acute lithium response. Clinical features associated with favorable lithium response include family history of lithium response (P. Grof et al., 2002), pure mania with minimal concurrent depressive symptoms (Swann et al., 1997), and relatively few lifetime mood episodes (Swann et al., 1999).

Lithium has been compared with first-generation (typical) antipsychotic agents (FGAs) in nine controlled trials in the treatment of acute bipolar mania (Garfinkel, Stancer, & Persad, 1980; Johnson, Gershon, Burdock, Floyd, & Hekiman, 1971; Johnson, Gershon, & Hekiman, 1968; Platman, 1970; Prien, Caffey, & Klett, 1972; Segal, Berk, & Brook, 1998; Shopsin, Gershon, Thompson, & Collins, 1975; Spring, Schweid, Gray, Steinberg, & Horwitz, 1970; Takahashi, Sakuma, Itoh, Itoh, & Kurihara, 1975). Interpretation of the results of some of these studies is difficult due to the inclusion of manic patients with schizoaffective disorder; the lack of standardized rating scales for mania; lack of use of last observation carried forward or comparable analyses; and the possibility of a type II error (failure to find a significant difference between treatments because of insufficient sample size; Johnson, Gershon, & Hekiman, 1968; Johnson et al., 1971; Platman, 1970; Segal et al., 1998; Shopsin et al., 1975). Two studies also titrated lithium to serum concentrations to the low end of the therapeutic range (Shopsin et al., 1975; Takahashi et al., 1975). Common side effects associated with lithium in these studies were nausea, vomiting, tremor, somnolence, weight gain, and cognitive slowing.

In summary, data from the controlled trials reviewed above indicate that lithium is superior in efficacy to placebo, with an onset of action within 7 to 10 days with gradual titration, and usually requires a 2- to 4-week trial at therapeutic levels to reach maximum effect. These data also suggest that lithium is superior to FGAs for amelioration of mood symptoms and exerts improvement in psychosis in tandem with improvement in the overall manic syndrome (Prien et al., 1972). On the other hand, FGAs had a more rapid onset of action and were more effective initially in agitated patients (Prien et al., 1972).

First-Generation (Typical) Antipsychotics

Prior to the introduction of lithium, antipsychotic medications were one of the few available classes of medications for the treatment of acute mania and as maintenance treatment for patients with bipolar disorder (Baldessarini, 1985). However, the emergence of lithium, valproate, carbamazepine, and second-generation antipsychotics (SGAs, atypicals) has limited the role of FGAs to the acute treatment of psychotic mania or psychotic depression in conjunction with thymoleptic agents. This is due in part to the neurological and neuroendocrinological side effects associated with FGAs as well as evidence that their use may increase the risk of postmanic depressive episodes, compared with SGAs. There is one double-blind, placebo-controlled trial of an FGA, chlorpromazine, in the treatment of bipolar mania (Klein, 1967). Not surprisingly, chlorpromazine (1,200 mg/day) was superior to imipramine (300 mg/day) or placebo in a 7-week trial involving only 13 patients rated globally for improvement. Most other studies examining FGAs in the treatment of acute mania have included these agents as active comparators in trials of lithium, valproate, carbamazepine, or SGAs reviewed elsewhere in this chapter.

Valproate

Valproate and its divalproex formulation have been shown to be effective in the treatment of acute mania in nine controlled trials (Bowden et al., 1994; Brennan, Sandyk, & Borsook, 1984; Emrich, Von Zerssen, & Kissling, 1981; Freeman, Clothier, Pazzaglaia, Lesem, & Swann, 1992; Hirschfeld, Allen, McEvoy, Keck, & Russell, 1999; Pope, McElroy, Keck, & Hudson, 1991; Post, Berretini, Uhde, & Kellner, 1984; Tohen et al., 2002a; Zajecka et al., 2002). These nine studies include comparisons of valproate with placebo in crossover trials (Brennan et al., 1984; Emrich et al., 1981; Post et al., 1984), with placebo in a parallel-group trial in treatment-refractory patients (Pope et al., 1991), with lithium in two parallel-group trials (Freeman et al., 1992; Hirschfeld et al., 1999), with placebo and lithium in a parallel-group trial (Bowden et al., 1994), and with olanzapine in two parallel-group trials (Tohen et al., 2002a; Zajecka et al., 2002).

In the most rigorous placebo-controlled trials, response rates to valproate ranged from 48% (Bowden et al., 1994) to 53% (Pope et al., 1991). The onset of antimanic response was evident by day 7 in each trial, despite gradual titration from baseline. Both lithium comparison trials were underpowered to detect a potential difference in efficacy between the two agents (Freeman et al., 1992; Hirschfeld et al., 1999). Nevertheless, Freeman and colleagues (1992) reported that patients with mixed mania were more likely to respond to valproate than to lithium. This observation is consistent with a post hoc analysis of findings from the study by Bowden and colleagues (1994) reported by Swann and colleagues (1997). Two randomized placebo-controlled trials examined the efficacy of the extended-release formulation of divalproex in patients with acute bipolar mania (Bowden et al., 2006; Hirschfeld et al., 2010). One study found significantly greater efficacy of this formulation in reduction in manic symptoms compared with placebo (Bowden et al., 2006); however, the second trial (Hirschfeld et al., 2010) did not, with possible limitations in this latter trial of high dropout rates (>80%) and lower-than-expected dosing.

Hirschfeld and colleagues (1999), and Hirschfeld, Baker, Wozniak, Tracy, and Sommerville (2003) specifically addressed the tolerability of divalproex oral loading (30 mg/kg per day for 2 days, then 20 mg/kg per day) and observed no significant differences in adverse events among patients randomized to divalproex loading, divalproex gradual titration, or lithium gradual titration. These findings confirmed earlier observations from open trials suggesting that divalproex oral loading was well tolerated (Keck, McElroy, Tugrul, & Bennett, 1993; McElroy, Keck, Tugrul, & Bennett, 1993; McElroy et al., 1996a).

Divalproex was compared with olanzapine in two head-to-head trials (Tohen et al., 2002a; Zajecka et al., 2002). Tohen and colleagues (2002a) found a significantly greater mean reduction in manic symptoms in patients treated with olanzapine compared with divalproex at 3 weeks. In contrast, Zajecka and colleagues (2002) did not find significant differences in efficacy between the two agents at 3 weeks. Both studies found overall better tolerability in patients receiving divalproex compared with olanzapine. These studies differed in the starting dose of each agent and in sample size. Tohen and colleagues (2002a) compared olanzapine 15 mg/day as a starting dose with divalproex gradual titration in a study adequately powered to yield significant differences in efficacy. Zajecka and colleagues (2002) compared divalproex loading with

olanzapine 10 mg/day as a starting dose in a study not adequately powered to yield potentially significant differences in efficacy. Taken together, the results of these two trials suggest that olanzapine may have a slight edge over divalproex in short-term efficacy in acute mania, but divalproex may have a slight edge in tolerability.

McElroy and colleagues (1996a) compared divalproex loading with haloperidol in an open randomized trial specifically in patients with psychotic mania. There were no significant differences in mean improvement in manic or psychotic symptoms between the two treatment groups. The improvement in psychosis observed with divalproex was consistent with findings in other studies (Bowden et al., 1994; Pope et al., 1991), and with improvement in manic psychosis with lithium in earlier studies.

Valproate has been studied as treatment adjunctive to FGAs in the treatment of acute bipolar mania (Muller-Oerlinghausen, Retzow, Henn, Giedke, & Walden, 1999). In this multicenter, double-blind, parallel-group, three-week trial, 136 patients receiving FGAs were randomized to valproate or placebo. By study endpoint, significantly more valproate-treated patients displayed a decrease in the need for concomitant antipsychotic medications. In summary, data from the controlled trials reviewed above indicate that valproate has a broad spectrum of efficacy in acute manic and mixed episodes, with or without psychosis, and appears to be comparable to lithium in overall antimanic efficacy.

Lastly, McElroy and colleagues (2010a) reported superior efficacy of divalproex extended-release loading monotherapy compared with placebo among outpatients with bipolar spectrum disorder displaying moderate to severe hypomania or mild mania.

Valproate-associated side effects in these studies include somnolence, nausea, vomiting, tremor, weight gain, and cognitive slowing. Rare serious side effects include hepatic transaminase elevations, hepatic failure, pancreatitis, thrombocytopenia, polycystic ovarian syndrome, and hyperammonemic encephalopathy in patients with urea cycle disorders.

Carbamazepine

Although a number of double-blind controlled trials provided preliminary evidence of carbamazepine's efficacy in the treatment of acute mania (Keck, McElroy, & Nemeroff, 1992), these findings were substantiated only several years later by large, multicenter, randomized, placebo-controlled, parallel-group trials (Weisler et al., 2004, 2005). In the first such trial, Weisler and colleagues (2004) randomized 204 inpatients hospitalized for a manic or mixed episode to an extended-release formulation of carbamazepine or placebo over 3 weeks. The carbamazepine-treated patients displayed significantly greater mean improvement in manic symptoms compared with patients receiving placebo by day 14. In addition, significantly more patients in the carbamazepine group were responders (42%) compared with the placebo group (22%). In a subgroup analysis, there was no significant difference in mean reduction of manic symptoms in patients with mixed episodes who received carbamazepine compared with placebo, due in part to a high placebo response in this subgroup.

Weisler and colleagues (2005) conducted a second, similar trial in which 239 bipolar inpatients with manic or mixed episodes were randomized to extended-release carbamazepine or placebo for up to 3 weeks. In this trial, patients in the carbamazepine group displayed a significantly greater mean reduction in manic symptoms compared with patients receiving placebo beginning at the time of the first rating following baseline, corresponding to day 7. At study end point, 61% of patients receiving carbamazepine were responders compared with 29% receiving placebo (last observation carried forward, day 21).

Unlike the first trial (Weisler et al., 2004), response rates were significantly greater in both manic and mixed patients receiving carbamazepine compared with placebo. Aside from the subgroup analyses in these two trials, there are no consistent data regarding clinical predictors of acute response to carbamazepine.

Carbamazepine has been compared with lithium (Lerer, Moore, Meyendorff, Cho, & Gershon, 1987, Small, 1990) and chlorpromazine (Grossi, Sacchetti, & Vita, 1984; Okuma et al., 1979) in head-to-head trials. These studies, although individually limited by sample sizes likely too small to detect significant differences in efficacy, nevertheless found generally comparable antimanic activity among patients receiving carbamazepine, lithium, or chlorpromazine.

Somnolence, fatigue, diplopia, blurred vision, and ataxia were commonly reported side effects of carbamazepine. Rare serious side effects include agranulocytosis, aplastic anemia, thrombocytopenia,

pancreatitis, hepatic failure, and Stevens-Johnson syndrome and toxic epidermal necrolysis. These latter systemic cutaneous reactions appear to be more common among individuals with the HLA-B*1502 allele, which, in turn, is prevalent among Asian and South Asian Indians (Hung et al., 2006). The FDA now recommends testing for the presence of this allele in these higher-risk ethnic groups.

Risperidone and Paliperidone

The efficacy of risperidone in the treatment of acute bipolar manic and mixed episodes has been established as monotherapy in two randomized, placebo-controlled trials (Hirschfeld et al., 2004; Khanna et al., 2005); as adjunctive therapy with lithium or divalproex in one placebo-controlled trial (Sachs, Grossman, Ghaemi, Okamato, & Bowden, 2002) and one open-label trial (Vieta et al., 2002a); and in comparison trials with olanzapine, haloperidol, and lithium (Brown, Ahmed, & Schuh, 2004; Segal et al., 1998; Smulevich et al., 2005). Risperidone was not superior to placebo in combination with lithium, carbamazepine, or divalproex in one trial (Yatham, Grossman, Augustyns, Vieta, & Ravindran, 2003). However, since this study included patients receiving carbamazepine, it is possible that there may have been significant reductions in plasma risperidone concentrations in these patients, undermining risperidone's efficacy. Hirschfeld and colleagues (2004) observed a significant mean reduction in manic symptoms by day 3 of the 3-week trial. In addition, risperidone exerted comparable efficacy in patients with manic and mixed episodes and with or without psychotic symptoms. Risperidone treatment was associated with low rates of extrapyramidal side effects when administered at average doses of less than 4 mg/day (Hirschfeld et al, 2004; Sachs et al., 2002; Yatham et al., 2003) but not when administered at average doses of 6 mg/day (Khanna et al., 2005; Segal et al., 1998).

Two placebo-controlled trials of paliperidone (9-hydroxyrisperidone), an active metabolite of risperidone, in acute bipolar mania yielded mixed findings (Berwaerts et al., 2012; Vieta et al., 2010a). Vieta and colleagues (2010a) found significantly higher remission rates among manic and mixed patients receiving paliperidone flexibly dosed 3 to 12 mg/day (52%) compared with placebo (29%). However, Berwaerts and colleagues (2012) found no differences in remission rates among patients randomized to receive placebo (37%) or paliperidone at fixed doses of 3 mg/day (37%), 6 mg/day (42%) or 12 mg/day (45%). It is possible that the multiple arms of this fixed-dose trial contributed to higher-than-expected placebo response rate. Berwaerts and colleagues (2011) compared paliperidone with placebo as an adjunctive treatment to lithium or valproate in patients with an inadequate response to these latter agents as monotherapy, but there was no significant difference in outcome measures between the paliperidone and placebo groups.

Common side effects from risperidone and paliperidone include akathisia, extrapyramidal signs, somnolence, appetite increase, weight gain, nausea, and prolactin elevation.

Olanzapine

In monotherapy trials, olanzapine was superior to placebo (Tohen et al., 1999, 2003) and divalproex (Tohen et al., 2002a), and comparable to lithium (Berk, Ichim, & Brook, 1999), divalproex (Zajecka et al., 2002), haloperidol (Tohen et al., 2003a), and risperidone (Brown et al., 2004) in mean improvement in manic symptoms in randomized controlled trials ranging from 3 to 6 weeks. Olanzapine-treated patients displayed significantly greater improvement in manic symptoms compared with patients receiving placebo by day 7 in one trial (Tohen et al., 2000), and day 21 in another (Tohen et al., 1999). The addition of olanzapine was also superior to placebo in patients who had partially responded to lithium or divalproex monotherapy for at least 2 weeks (Tohen et al., 2002b). There were no significant differences among patients with manic or mixed, rapid or nonrapid cycling or psychotic or nonpsychotic symptoms in studies in which sample sizes allowed post hoc comparisons (Baldessarini, Tondo, & Hennen, 2003). Initial starting doses of 15 mg/day appeared to exert more rapid antimanic efficacy compared with 10 mg/day (Tohen et al., 1999, 2000). In addition, one study found significant improvement in agitation within 1 day in patients receiving olanzapine alone in doses of 20 to 40 mg/day compared with 10 mg/day augmented by benzodiazepine use (Baker, Kinon, Maguire, Liu, & Hill, 2003). These results are consistent with a study of the intramuscular formulation of olanzapine, in which patients receiving olanzapine 10 mg given

intramuscularly displayed significant reductions in manic agitation within 2 hours of administration compared with patients receiving intramuscular placebo (Meehan et al., 2001).

Olanzapine-associated side effects in clinical trials were somnolence, constipation, appetite increase, weight gain, metabolic syndrome, headache, dry mouth, and dizziness.

Quetiapine

Quetiapine was superior to placebo in two monotherapy 12-week trials (Bowden et al., 2005; McIntyre, Brecher, Paulsson, Huizar, & Mullen, 2005) and in three studies in combination with lithium or divalproex (DelBello, Schwiers, & Rosenberg, 2002; Sachs et al., 2004; Yatham et al., 2004), and comparable to divalproex in one head-to-head comparison in adolescents (DelBello et al., 2006). The two placebo-controlled monotherapy trials also included active comparators of lithium (Bowden et al., 2005) or haloperidol (McIntyre et al., 2005). In these trials, there was no significant difference in efficacy between patients receiving quetiapine and either lithium or haloperidol, although the studies were not powered to detect such a difference if one existed. Significant differences in efficacy in favor of quetiapine over placebo were evident by day 4 in the two monotherapy trials, and patients receiving quetiapine displayed cumulative improvement in manic symptoms at 3 and 12 weeks (Vieta, Mullen, Brecher, Paulsson, & Jones, 2005b). The mean modal dose of quetiapine associated with antimanic efficacy in most studies was approximately 600 mg/day (Vieta et al., 2005b). Many of these trials excluded patients with mixed episodes (Bowden et al., 2005; McIntyre et al., 2005; Sachs et al., 2004; Yatham et al., 2004), so a comparative analysis of response between manic and mixed patients could not be conducted. There were no significant differences in response rates to quetiapine in patients with or without psychotic symptoms (Vieta et al., 2005b).

The emergence of hypomanic or mild manic symptoms in patients with bipolar I disorder or with other bipolar spectrum disorders presents a common clinical challenge but until recently had not been systemically studied in a controlled treatment trial. In an 8-week study among outpatients with bipolar spectrum moderate to severe hypomania or mild mania, quetiapine monotherapy (mean dose 232 mg/day) was marginally superior to placebo ($p = 0.06$) in reduction of Young Mania Rating Scale (YMRS) scores and significantly better than placebo in measures of overall global improvement and global improvement in manic symptoms (McElroy et al., 2010b). In a similar trial, the anxiolytic effects of extended-release quetiapine (50 to 300 mg/day) were compared with extended-release divalproex (500 to 3000 mg/day) and placebo in an 8-week, double-blind trial of outpatients with bipolar disorder and co-occurring generalized anxiety or panic disorder (Sheehan et al., 2013). The extended-release quetiapine (mean dose 186 mg/day) displayed significantly greater improvement in a measure of anxiety compared with the extended-release divalproex and placebo groups.

Side effects associated with quetiapine in acute bipolar mania trials included somnolence, constipation, weight gain, metabolic syndrome, headache, dry mouth, and dizziness.

Ziprasidone

In two 3-week, placebo-controlled, monotherapy trials, ziprasidone (mean dose 120 to 130 mg/day) produced significant reductions in manic symptoms by day 2 of treatment (Keck et al., 2003c; Potkin, Keck, Segal, Ice, & English, 2005). Ziprasidone-treated patients also had significantly higher response rates compared with patients receiving placebo. Vieta and colleagues (2010b) conducted a 12-week, haloperidol- and placebo-controlled trial (with efficacy assessment at week 3 and a 9-week extension active treatment comparison phase). Both ziprasidone and haloperidol groups had significantly greater improvement in manic symptoms, with greater efficacy for haloperidol, compared with placebo. In the 9-week extension, responses were maintained comparably for patients continuing to receive haloperidol (mean dose 16 mg/day) or ziprasidone (mean dose 121 mg/day), with better tolerability and lower discontinuation rates associated with ziprasidone. Ziprasidone was equally effective in patients with manic and mixed episodes and with and without psychotic symptoms.

Ziprasidone was not superior to placebo as an adjunctive treatment with lithium in a study designed to prove superior onset of action by day 14 (Weisler, Dunn, & English, 2003). However, patients receiving ziprasidone in combination with lithium had

significantly greater improvement in manic symptoms by day 4 compared with patients receiving placebo in combination with lithium. A second placebo-controlled, adjunctive trial to lithium and divalproex, designed to assess efficacy from baseline to week 3 of treatment, also found no significant difference in efficacy between the two study groups (Sachs et al., 2012a). However, enrollment of a substantial proportion of patients who did not meet eligibility criteria may have contributed to the negative findings in this study (Sachs et al., 2012b).

Common side effects associated with ziprasidone in studies of its efficacy and safety in acute bipolar mania were dizziness, akathisia, extrapyramidal signs, somnolence, and headache.

Aripiprazole

Aripiprazole was superior to placebo in three 3-week randomized controlled trials in patients with manic and mixed episodes (Kanba et al., 2012; Keck et al., 2003a) and comparable in efficacy to haloperidol in two twelve-week, adequately powered comparison trials (Vieta et al., 2005a; Young et al., 2009), one of which (Young et al., 2009) included a placebo arm wherein both active agents were comparably superior. In a fixed-dose, three-arm, aripiprazole, placebo-controlled trial there was no significant difference in efficacy between the aripiprazole and placebo groups (El Mallakh et al., 2010). In the three positive trials, initial target doses ranged from 24 to 30 mg/day with good tolerability, and patients displayed significantly greater improvement in manic symptoms compared with placebo by day 4 of both trials. The aripiprazole groups also had significantly higher response rates compared with the placebo groups. The mean dose of aripiprazole in the haloperidol comparison was 23 mg/day. There were no significant differences in response to aripiprazole among patients with manic and mixed episodes, and with or without psychotic symptoms. Adjunctive aripiprazole was superior to placebo in reduction of manic symptoms from week 1 on in a 6-week trial in patients with bipolar mania who had an inadequate response to lithium or valproate monotherapy at therapeutic concentrations (Vieta et al., 2008b).

Common aripiprazole side effects in these short-term trials were headache, nausea, vomiting, constipation, insomnia, and akathisia.

Asenapine

In two 3-week, double-blind, placebo-controlled trials of asenapine (mean dose 18 mg/day) in the treatment of acute manic or mixed episodes, each with an olanzapine noninferiority comparison arm, patients receiving asenapine displayed significantly greater improvement in manic symptoms as measured by the YMRS compared with the placebo group, with differences evident by day 2 (McIntyre et al., 2009a, 2010). Patients with manic and mixed symptoms had comparable improvement with asenapine. However, there were no significant differences between the asenapine and placebo groups in response or remission rates in these two studies, and olanzapine efficacy was superior to asenapine. In a 12-week, placebo-controlled, adjunctive treatment trial, adding asenapine to lithium or valproate was superior to placebo addition (Szegedi et al., 2012).

Asenapine-associated side effects reported in these trials included somnolence, insomnia, extrapyramidal signs, headache, akathisia, dizziness, weight gain, and triglyceride elevation.

Other Agents

Cariprazine (mean dose 7.4 mg/day; modal dose 12 mg/day), a dopamine D_2/D_3 partial agonist, was superior to placebo in three, 3-week, placebo-controlled trials in patients with bipolar manic and mixed episodes in reduction of manic symptoms as measured by the YMRS, and in response rates (Keck et al., 2013). Cariprazine side effects reported were headache, nausea, vomiting, constipation, insomnia, and akathisia. At press, this agent is not yet approved for this indication by the FDA. The protein kinase C (PKC) inhibitor, tamoxifen, approved for the treatment of breast cancer, has been reported to exert significant antimanic efficacy in two pilot monotherapy trials (Yildiz et al., 2008; Zarate et al., 2007) and one adjunctive therapy trial in patients receiving lithium (Amrollahi et al., 2010). These intriguing results indicate the need for a large, definitive trial, addressing in particular optimal dosing and duration of treatment. Similarly intriguing preliminary findings have been reported for adjunctive allopurinol, a xanthine oxidase inhibitor approved for the treatment of gout, compared with placebo in the treatment of acute mania (Akhondzadeh et al., 2006; Machado-Vieira et al., 2008). In an 8-week, placebo-controlled trial, allopurinol was superior to placebo added to lithium and haloperidol in 82 patients

hospitalized for acute mania (Akhondzadeh et al., 2006). In the second study, adjunctive allopurinol was superior to placebo in a trial that also included a dipyramidole arm, each added to lithium over 4 weeks (Machado-Vieira et al., 2008).

N-acetyl cysteine (NAC), a glutamate modifying drug that is available both by prescription and over the counter, was compared with placebo in a small ($N = 15$) pilot, 24-week, placebo-controlled trial in patients with manic symptoms (Vieira et al., 2013). The NAC group demonstrated an improvement in manic symptoms with worsening of depressive symptoms in the placebo group.

In randomized controlled trials in patients with acute bipolar mania, several agents have failed to demonstrate significant antimanic activity to date. These agents include gabapentin (Frye et al., 2000; Pande, Crockatt, Janney, Werth, & Tsaroucha, 2000), topiramate (McElroy & Keck, 2004a), and verapamil (Janicak, Sharma, Pandey, & Davis, 1998; Walton, Berk, & Brook, 1996). In addition, several agents—lamotrigine (Anand, Oren, & Berman, 1999; Frye et al., 2000; Ichim, Berk, & Brook, 2000), oxcarbazepine (Emrich, Dose, & VonZerssen, 1985; Muller & Stoll, 1984; Wagner et al., 2006), tiagabine (Grunze et al., 1999; Suppes et al., 2002), and levetiracetam (Bersani 2004; Braunig & Kruger, 2003; Grunze, Langosch, Born, Schaub, & Walden, 2003; Post et al., 2005)—have been studied in randomized controlled trials that have yielded mixed or insufficient evidence of antimanic efficacy thus far.

Akhondzadeh, Mohajari, Reza, and Amini (2003) conducted a randomized, placebo-controlled trial of the 5-HT_2 antagonist ritanserin as adjunctive treatment with lithium and haloperidol in 45 treatment-naïve patients with acute bipolar mania. Patients receiving adjunctive ritanserin had significantly better improvement in manic symptoms and had lower rates of extrapyramidal side effects compared with patients receiving adjunctive placebo. These intriguing findings require replication.

PSYCHOPHARMACOLOGICAL TREATMENTS FOR ACUTE BIPOLAR DEPRESSION

Lithium and Antidepressants

After years of being understudied, the pharmacological treatment of bipolar depression received renewed attention in a number of recent type 1 randomized controlled trials (Keck, McElroy, & Nelson, 2003b). The majority of controlled trials to date have assessed the efficacy of lithium in comparison to placebo or tricyclic antidepressants (Baron, Gershon, Rudy, Jonas, & Buchshaum, 1975; Donnelly, Goodwin, Waldman, & Murphy, 1978; Fieve, Platman, & Plutchnik, 1968; Goodwin et al., 1969; Goodwin, Murphy, Dunner, & Bunney, 1972; Greenspan, Schildkraut, Gordon, Levy, & Durrell, 1979; Keck, Welge, Strakowski, Arnold, & McElroy, 2000b; Mendels, 1976; Nemeroff et al., 2001; Noyes, Dempsey, Blum, & Cavenaugh, 1974; Stokes et al., 1971). All but one (Nemeroff et al., 2001) of these placebo-controlled trials used crossover designs with short time intervals, ranging from 1 to 28 days of lithium or placebo exposure. These short intervals limit the interpretation of the study results because of the potential confounding effects of lingering lithium activity during the placebo period and because optimal lithium response may have required a longer trial (Zornberg & Pope, 1993). Abrupt discontinuation of lithium may have contributed to a more rapid rate of episode recurrence than that attributable to the natural course of the illness (Suppes, Baldessarini, Faedda, & Tohen, 1991). Moreover, these studies did not exclusively enroll patients with bipolar depression, and they did not report switch rates into hypomania, mania, or mixed states. Primary outcome measures were also often not specified at the outset of these trials (Muzina & Calabrese, 2003). With these limitations in mind, pooled results from five crossover studies that provided sufficient data to assess degree of response revealed that 29 (36%) of 80 patients with acute bipolar depression displayed an unequivocal response to lithium; 63 (79%) patients had at least partial improvement (Zornberg & Pope, 1993).

Two controlled studies assessed the efficacy of lithium against tricyclic antidepressant monotherapy (Donnelly et al., 1978; Watanabe, Ishino, & Otsuki, 1975). Neither trial found significant differences in efficacy between patients receiving lithium or imipramine. A number of other controlled studies examined the efficacy of tricyclics in comparison to other classes of antidepressant agents (Altshuler et al., 1995; Ashberg-Wistedt, 1982; Baumhackl et al., 1989; Cohn, Collins, Ashbrook, & Wernicke, 1980; Himmelhoch, Thase, Mallinger, & Houck, 1991; Kessel & Holt, 1975; Levine et al., 1995; Nemeroff et al., 2001; Sachs et al., 1994; Silverstone, 2001).

The most recent trial comparing imipramine, paroxetine, or placebo added to lithium for breakthrough bipolar depressive episodes did not find a significant difference in acute efficacy among the three groups (Nemeroff et al., 2001). A post hoc analysis revealed that patients with lithium levels of less than 0.8 mEq/L displayed significantly greater improvement in depressive symptoms when randomized to paroxetine compared with placebo. However, in patients with lithium levels greater than 0.8 mEq/L, there were no significant differences in mean reduction of depressive symptoms. Two previous controlled trials comparing serotonin reuptake inhibitor (SRI) antidepressants with tricyclics had significant methodological limitations (Ashberg-Wistedt, 1982; Cohn et al., 1980). In the first study, a double-blind, randomized comparison of fluoxetine and imipramine with placebo, only 64 (72%) of 89 patients remained in the trial after 3 weeks, and only 44 (49%) completed the 6-week study because of side effects or lack of efficacy (Cohn et al., 1980). Furthermore, 7 (16%) subjects completing the study received lithium, but the remainder did not. If treatment dropouts were counted as treatment failures, the response rates in this study were not significantly different for fluoxetine (60%) and imipramine (40%). Both were superior to placebo. The second SRI comparison trial involved only 4 patients in a 4-week crossover trial of zimelidine and desipramine, with no conclusive findings due to the small sample size (Ashberg-Wistedt, 1982).

Two studies compared tricyclic antidepressants with reversible MAOIs (Baumhackl et al., 1989; Silverstone, 2001) and one with an irreversible MAOI (Himmelhoch et al., 1991). In the most methodologically rigorous of these studies, tranylcypromine had significantly greater efficacy than imipramine in 56 patients (bipolar I, $N = 24$; bipolar II, $N = 32$) treated for 4 weeks without lithium or another mood stabilizer (Himmelhoch et al., 1991). Of 26 tranylcypromine-treated patients, 21 (81%) displayed a significant antidepressant response compared with 10 (48%) of 21 imipramine-treated patients. Response rates did not differ between bipolar I and bipolar II patients. Silverstone (2001) compared the reversible MAO-A inhibitor moclobemide with imipramine, either as monotherapy or added to ongoing mood stabilizers, in an 8-week trial of 156 patients (75% outpatients) with bipolar I depression. In the moclobemide group, 46% of patients were receiving lithium (two in combination with carbamazepine). In the imipramine group, 49% were receiving lithium (five in combination with carbamazepine and one with valproate). Both treatment groups had significant mean reductions in depressive symptoms from baseline, but without a significant difference in efficacy between groups. More patients switched into mania in the imipramine group (11%) than in the moclobemide group (4%), and they switched earlier in treatment, although these differences were not significant. The authors did not report whether switches occurred less commonly among patients receiving mood stabilizers. Baumhackl and colleagues (1989), in an earlier, smaller ($N = 32$), 4-week, monotherapy comparison trial between moclobemide and imipramine, similarly failed to find a significant difference in efficacy between the two agents.

A number of other small pilot trials of antidepressants, usually in combination with mood stabilizers, have been conducted in patients with bipolar depression. Young and colleagues (2000) compared the efficacy of adjunctive paroxetine with a second mood stabilizer (lithium or divalproex) in a 6-week trial in 27 outpatients with breakthrough bipolar depressive episodes (type I, $N = 11$; type II, $N = 16$) despite treatment with therapeutic doses of lithium or divalproex for at least 3 months. In the combination mood stabilizer group, patients receiving lithium were randomized to divalproex and vice versa. Both adjunctive treatment groups displayed significant reductions in depressive symptoms, but without significant differences in efficacy between groups. Because of the small sample size and the limited duration of the trial, no conclusions could be reached about the relative efficacy of the different strategies.

Kessel and Holt (1975) compared maprotiline and imipramine in 14 patients for 6 weeks, with no significant differences in response rates. Sachs and colleagues (1994) compared desipramine with bupropion in 19 patients with bipolar I depression and found that although both agents produced comparable response rates, patients treated with desipramine (50%) were significantly more likely to switch into hypomania or mania than patients receiving bupropion (10%).

Two preliminary placebo-controlled, randomized adjunctive trials assessed the efficacy and safety of the dopamine D_2/D_3 receptor agonist pramipexole in the treatment of bipolar I and bipolar II depressed patients (Goldberg, Burdick, & Endick, 2004; Zarate et al., 2004b). Goldberg and colleagues (2004) randomized 22 patients (bipolar I, $N = 15$; bipolar II,

N = 7) to pramipexole (mean maximum dose, 1.7 mg/day) or placebo added to existing mood stabilizers for 6 weeks. Eight (67%) patients receiving pramipexole and two (20%) patients receiving placebo had more than a 50% reduction in depressive symptoms at study endpoint. Pramipexole-treated patients also had greater improvement in mean percentage reduction of depressive symptoms from baseline compared with patients receiving placebo. One patient in the pramipexole group experienced hypomanic symptoms, compared with none in the placebo group. Zarate and colleagues (2004b) conducted a 6-week trial of similar design except that only patients with bipolar II disorder were included (N = 21). The response rate (greater than 50% improvement in depressive symptoms from baseline) was significantly higher in the pramipexole group (60%) compared with the placebo group (9%). One patient on pramipexole and two on placebo experienced hypomanic symptoms. These intriguing findings suggest that pramipexole may have efficacy as an adjunctive treatment for bipolar depression and are consistent with open-label reports in patients with bipolar (Perugi, Ruffolo, Frare, & Toni, et al., 2001; Sporn, Ghaemi, Sambur, & Rankin, 2000) and unipolar depression (Lattanzi et al., 2002; Sporn et al., 2000).

Antidepressant-induced mood switching or cycle acceleration is an important risk of antidepressant treatment in patients with bipolar depression. Reported switch rates among patients with bipolar depression treated with antidepressants have ranged widely, from 4% to 70% (Sachs, Koslow, & Ghaemi, 2000). These disparate estimates reflect differences in data collected from naturalistic compared with controlled trials, whether or not patients were receiving concomitant mood stabilizers, the duration of study, and the specific type of antidepressant and mood stabilizer combinations. A number of studies have attempted to clarify the switch rates and the degree to which mood stabilizers reduce this risk in patients with bipolar depression. Bottlender and colleagues (2001) reviewed the medical records of 158 patients with bipolar I depression to determine the incidence of mania and hypomania in relation to treatment. The overall switch rate was 25%. Among those patients who experienced a mood switch, 80% were receiving tricyclic antidepressants, a significantly higher proportion than those not switching who were not receiving tricyclics (51%). Overall switch rates were 34% for patients receiving tricyclic agents, 12% for those receiving SRIs, 8% for MAOIs, and 14% for other agents. The protective effect of a mood stabilizer was most apparent for patients receiving tricyclics, in whom twice as many switched when not receiving a concomitant mood stabilizer. These findings are consistent with earlier studies suggesting that co-administration of lithium reduced the risk of antidepressant-associated switching by approximately 50% (Boerlin, Gitlin, Zoellner, & Hammen, 1998; Henry, Sorbara, Lacoste, Gindre, & Leboyer, 2001; Prien et al., 1984; Rouillon, Lejoyeaux, & Filteau, 1992).

Post and colleagues (Post et al., 2001, 2004) analyzed switch data from the Stanley Foundation Bipolar Network trial comparing adjunctive sertraline, bupropion, or venlafaxine with mood stabilizers in patients with bipolar depression. Thirteen (14%) of 95 patients experienced a mood switch during the 10-week acute treatment trial: 7% into hypomania and 7% into mania. During the subsequent maintenance trial up to 1 year, 33% switched: 20% into hypomania and 13% into mania (Post et al., 2001). The switch rate with venlafaxine was slightly but significantly higher than with the other two agents (Post et al., 2004). This finding is consistent with an earlier report by Vieta and colleagues (2002b), who also found a higher switch rate in patients receiving adjunctive venlafaxine compared with paroxetine in an open-label comparison trial. Because of the lack of placebo control groups in these studies, it is difficult to compare these rates with those associated with spontaneous rates from the illness, but the switch rates into mania were lower than anticipated.

In a meta-analysis of the rate of treatment-emergent switch into mania, with data derived from clinical trials comparing SRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline), tricyclics, or placebo in 415 patients with bipolar depression, Peet (1994) reported that manic switch occurred significantly more commonly with tricyclics (11%) than with SRIs (4%) or placebo (4%). Data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) revealed that among 338 patients with bipolar disorder and with prior antidepressant treatment, 44% reported at least one switch into mania or hypomania associated with antidepressant treatment (Truman et al., 2007). Predictors of increased switch risk were a shorter duration of illness and a history of multiple antidepressant trials. Among classes of antidepressants, switch was least common with treatment with electroconvulsive therapy or MAOIs. Tricyclics

were associated with the highest risk, with intermediate risk from treatment with SSRIs or bupropion. These findings are limited by the retrospective, self-report nature of data collection. However, in prospectively gathered data, combination treatment with a mood stabilizer and an antidepressant was not superior to treatment with a mood stabilizer alone for patients with bipolar depression (Goldberg et al., 2007). Moreover, adjunctive antidepressant use was associated with significantly higher mania symptom severity at the 3-month follow-up assessment.

Quetiapine

Calabrese and colleagues (2005) examined the efficacy of quetiapine 300 mg/day, 600 mg/day, or placebo in an 8-week trial involving 542 outpatients with bipolar I (N = 360) or bipolar II (N = 182) depression. Both quetiapine groups had significantly greater improvement in depressive symptoms compared with the placebo group from week 1 onward. Responder rates (proportion of patients with greater than 50% improvement in depressive symptoms from baseline to endpoint) were also significantly higher in the quetiapine 300 mg/day (58%) and 600 mg/day (58%) groups compared with placebo (36%). Treatment-emergent mania rates were similar for the quetiapine (3%) and placebo (4%) groups. Patients with bipolar I depression had greater improvement with quetiapine compared with bipolar II patients. There were no significant differences in efficacy between the two quetiapine dosage groups, but the 300 mg/day group had better overall tolerability. Thase and colleagues (2006) replicated these findings in a nearly identically designed trial.

Two other pivotal double-blind, placebo-controlled, 8-week studies examined the efficacy and safety of quetiapine for patients with acute bipolar (I and II) depression (McElroy et al., 2010c; Young et al., 2010). The first trial compared quetiapine at 300 mg/day and 600 mg/day with lithium 600 to 1800 mg/day and placebo (Young et al., 2010). Patients in both quetiapine groups displayed significantly greater improvement in depressive symptoms, as well as overall improvement and reductions in anxiety symptoms compared with lithium and placebo. The second trial examined the same two doses but included a group receiving paroxetine 20 mg/day as well as a placebo group (McElroy et al., 2010c). Both quetiapine groups again had significantly greater improvement in depressive symptoms compared with paroxetine and placebo. The most common adverse events associated with quetiapine were somnolence, dry mouth, and dizziness. These results are consistent with the results seen in trials of quetiapine as monotherapy or adjunctive therapy in major depressive disorder (McIntyre et al., 2009b).

Olanzapine and Olanzapine–Fluoxetine Combination

Three controlled trials examined the efficacy of combination olanzapine and fluoxetine (Amsterdam & Shults, 2005; Brown et al., 2006; Tohen et al., 2003c). Tohen and colleagues (2003c) compared olanzapine (mean dose 9 mg/day), the combination of olanzapine (mean dose 7 mg/day) and fluoxetine (mean dose 38 mg/day), and placebo in an 8-week trial in 833 patients with bipolar I depression. Both active treatment groups displayed significantly greater improvement in depressive symptoms than the placebo group, beginning at week 1. In addition, the olanzapine–fluoxetine group displayed significantly greater improvement in depressive symptoms compared with the olanzapine group at weeks 4, 6, and 8. There were no significant differences in switch rates: olanzapine 6%, olanzapine–fluoxetine 6%, placebo 7%. The response to olanzapine–fluoxetine in this study was also consistent with the antidepressant response reported by Shelton and colleagues (2001) for patients with treatment-refractory nonpsychotic major depressive disorder.

Amsterdam and Shults (2005) compared switch rates among patients with bipolar I (N = 32) and bipolar II (N = 2) depression randomized to fluoxetine (10 to 30 mg/day), olanzapine (5 to 20 mg/day), or olanzapine (5 to 15 mg/day) and fluoxetine (10 to 40 mg/day) combination for up to 8 weeks. They found comparable efficacy and induction of mania among all three treatment groups. These investigators also reported low switch rates in open-label monotherapy trials of venlafaxine (Amsterdam & Garcia-Espana, 2000) and fluoxetine (Amsterdam, Shults, Brunswick, & Hundert, 2004) in depressed patients with bipolar II and bipolar disorder not otherwise specified. Brown and colleagues (2006) conducted a 7-week, head-to-head comparison of olanzapine–fluoxetine with lamotrigine (titrated to 200 mg/day) in 205 depressed patients with bipolar I disorder. Patients receiving

olanzapine–fluoxetine had significantly greater improvement than lamotrigine-treated patients across the 7-week treatment period. The lamotrigine group may have had a greater response with a longer trial, given the need for gradual lamotrigine titration. There were no significant differences in switch rates between the olanzapine–fluoxetine (4%) and lamotrigine (5%) groups.

Tohen and colleagues (2012) examined the efficacy of olanzapine monotherapy (5 to 20 mg/day) compared with placebo in a 6-week randomized trial of patients with acute bipolar I depression. Patients receiving olanzapine had significantly greater improvement in depressive symptoms, overall improvement, and response and remission rates compared with the placebo group.

Lurasidone

Lurasidone has been examined in one monotherapy (Loebel et al., 2012a) and one adjunctive therapy (Loebel et al., 2012b) trial, each compared with placebo over six weeks in patients with bipolar I depression. In the monotherapy trial (Loebel et al., 2012a), two dose ranges (20 to 60 mg/day: mean modal dose 35 mg/day; 80 to 120 mg/day; mean modal dose, 91 mg/day) of lurasidone were compared with placebo. Lurasidone-treated patients in both study arms displayed significantly greater improvement in depressive and anxiety symptoms, measures of disability and quality of life, and response and remission rates compared with the placebo group. Side effects of nausea, akathisia, insomnia, somnolence, sedation, and dizziness occurred slightly more frequently in the higher-dosage-range group. In the adjunctive therapy trial (Loebel et al., 2012b), lurasidone (20 to 120 mg/day; mean dose, 66 mg/day) or placebo was added to lithium or valproate, each of which had been first maintained at therapeutic levels for at least 28 days without an adequate antidepressant response. The lurasidone group had significantly greater improvement in depressive and anxiety symptoms, measures of disability and quality of life, and response and remission rates. There were no significant differences in switch rates among the treatment groups in either trial.

Other Second-Generation Antipsychotics

Shelton and Stahl (2004) randomized 30 patients with bipolar I ($N = 21$) or bipolar II ($N = 9$) depression despite treatment with a stable and therapeutic dose of a mood stabilizer to adjunctive treatment with paroxetine, risperidone, or the combination over 12 weeks. All three groups displayed significant reductions in depressive symptoms from baseline to endpoint without significant differences among groups. One patient in the paroxetine group developed hypomanic symptoms during the trial. The results of this trial are limited by the small sample size, heterogeneity in mood stabilizer treatment, and significant difference in mean maximum paroxetine dose between the paroxetine group (35 mg/day) and the paroxetine–risperidone group (22 mg/day). The lower paroxetine dose in the combination group may have been due to inhibition of paroxetine metabolism by risperidone.

Two randomized, placebo-controlled, 8-week studies of aripiprazole monotherapy (10 mg/day, then flexibly dosed at 5 to 30 mg/day) for patients with bipolar I depression did not find greater efficacy of aripiprazole compared with placebo at study endpoint (Thase et al., 2008), despite significant differences in efficacy in favor of aripiprazole during weeks 1 to 6. Aripiprazole was associated with greater rates of akathisia, insomnia, nausea, fatigue, restlessness, and dry mouth. A small ($N = 23$) 6-week, adjunctive trial of aripiprazole compared with placebo in patients receiving lithium or valproate for at least one week and also openly treated with citalopram for 6 weeks (begun during the double-blind phase of the trial) found no difference in efficacy between the two groups (Quante et al. 2010). This results of this study are limited by the small sample size and potential confounding effects of citalopram.

Adjunctive ziprasidone (20 to 80 mg/day) did not separate from placebo in a 6-week randomized controlled trial, each added to patients receiving therapeutic doses of lithium, lamotrigine or valproate (Sachs et al., 2011). Possible methodological limitations identified post hoc included the enrollment of a substantial number of subjects with low diagnostic confidence, low quality of depressive symptom ratings, and by what the study authors described as "overzealous reporting of symptoms" by study subjects. These same methodological limitations may have affected the results of another, negative study in which ziprasidone adjunctive therapy did not separate from placebo in patients with bipolar I depression (Lombardo et al., 2012).

Lamotrigine

Two published randomized, placebo-controlled trials examined the efficacy of lamotrigine in the treatment of acute bipolar depression (Calabrese et al., 1999; Frye et al., 2000). Calabrese and colleagues (1999) randomized 195 patients with bipolar I depression to lamotrigine monotherapy 50 mg/day, 200 mg/day, or placebo. Both lamotrigine doses were superior to placebo. Although the difference between the two doses was not significant, there was a trend toward a modest advantage for the higher-dose group, an advantage that may have become more apparent with a longer trial, given the gradual titration required. Switch rates were not significantly different among the three groups: placebo, 5% lamotrigine 50 mg/day, 3% and lamotrigine 200 mg/day, 8%.

Frye and colleagues (2000), in a crossover trial previously described, reported that patients displayed significantly greater improvement in depressive symptoms while receiving lamotrigine (mean dose 274 mg/day) compared with placebo. The design of this trial did not allow for the examination of possible differences in switch rates. Taken together, the results of these two trials suggest that monotherapy with lamotrigine at 50 to 275 mg/day was efficacious in the treatment of bipolar depression.

Lamotrigine was compared with placebo as adjunctive treatment to lithium in an 8-week trial in patients with bipolar (I or II) depression (Van der Loos et al., 2009). Patients in the combination therapy group displayed significantly greater improvement in depressive symptoms and response rates compared with the placebo–lithium group, with no differences in switch rates into hypomania or mania.

Carbamazepine

Three small controlled studies evaluated the efficacy of carbamazepine in the treatment of patients with unipolar and bipolar depression (Kramlinger & Post, 1989; Post, Uhde, & Roy-Byrne, 1986; Small, 1990). In the first of these studies, a placebo-controlled crossover trial (median 45 days per treatment interval), Post and colleagues (1986) reported marked improvement in 12 (34%) of 35 patients (24 bipolar, 11 unipolar) with treatment-resistant depression. A trend toward greater improvement in patients with bipolar than unipolar depression was observed, and the switch to placebo was associated with deterioration in carbamazepine responders. In the second study, Small (1990) compared the response of 28 patients (4 bipolar, 24 unipolar) with treatment-resistant depression in a 4-week trial of lithium, carbamazepine, or their combination. All patients were then treated with both agents for an additional 4 weeks. Of patients receiving carbamazepine or the combination, 32% displayed moderate or marked improvement compared with 13% of lithium-only-treated patients. These results are consistent with those of Post and colleagues (1986), although the cohort studied by Small had significantly fewer bipolar patients. Finally, Kramlinger and Post (1989) evaluated the antidepressant effect of lithium versus placebo augmentation of carbamazepine and found that six (46%) of 13 patients who had not responded to carbamazepine alone responded to lithium augmentation.

Valproate

The antidepressant activity of divalproex has been examined in two small placebo-controlled trials in patients with bipolar depression (Davis, Bartolucci, & Petty, 2005; Sachs, Collins, & Altshuler, 2001). In a multisite study, Sachs and colleagues (2001) randomized 45 patients with bipolar disorder, type I, type II, and not otherwise specified, to divalproex (mean serum concentration, 62 mcg/mL) or placebo and found higher response rates in the divalproex group (43%) compared with the placebo group (27%). However, these differences were not significant, and there was no significant difference in mean reduction of depressive symptoms from baseline to endpoint between the two groups. The divalproex group had significantly greater improvement in depressive symptoms at weeks 2, 4, and 5 only. Davis and colleagues (2005) conducted a single-site, 8-week study of similar design involving 25 outpatients with bipolar I depression, but with a higher mean valproic acid concentration (81 mcg/mL). In this latter study, patients receiving divalproex had significantly greater reductions in depressive and anxiety symptoms than patients receiving placebo. These positive results require confirmation in a larger trial. Muzina and colleagues (2011) examined the efficacy of extended-release divalproex compared with placebo in depressed, predominantly rapid-cycling (67%) bipolar I and II patients in a 6-week trial. The divalproex group displayed significantly greater improvement in depressive symptoms from week 3 on compared with the placebo group.

Modafanil and Armodafanil

Armodafanil (150 mg/day) was compared with placebo in a large ($N = 257$) 8-week adjunctive trial in patients with bipolar I depression who had not responded to monotherapy with lithium, olanzapine, or valproate (Calabrese et al., 2010). Patients receiving armodafanil had significantly greater improvement in depressive symptoms compared with the placebo group. However, there were no significant differences between the groups on secondary outcome measures. Patients receiving armodafanil reported greater rates of headache, diarrhea, and insomnia. There was no difference in switch rates between the two groups. The results of this study are consistent with those of an earlier 6-week adjunctive trial of modafanil, which was superior to placebo in the reduction of depressive symptoms in patients with bipolar I and II disorder (Frye et al., 2007).

Other Agents

Two placebo-controlled trials evaluated the efficacy of formulations of omega-3 fatty acids in the treatment of bipolar depression (Keck et al., 2006b; Stoll et al., 1999). Stoll and colleagues (1999) reported significant improvement in depressive symptoms in patients who received a combination of EPA/DHA adjunctively or as monotherapy for 4 months compared with placebo. In contrast, Keck and colleagues (2006b) did not find significant efficacy for EPA 6 g/day compared with placebo used adjunctively with ongoing mood stabilizers.

In a study comparing inositol with placebo in patients with both bipolar and unipolar depression, Levine and colleagues (1995) found inositol superior to placebo in the overall group, but the number of patients with bipolar depression was too small ($N = 6$) to detect meaningful treatment effects.

Zarate and colleagues (2005) reported preliminary evidence that the glutamate-modulating agent riluzole was effective in improving depressive symptoms from baseline to endpoint when added to mood stabilizers in an open-label trial in 14 patients with bipolar I and II disorder. There were no switches into hypomania or mania. These results were consistent with similar open-label findings reported in patients with treatment-resistant major depressive disorder (Zarate et al., 2004a).

NAC 1 g/day, an orally bioavailable precursor to glutathione, was compared with placebo as adjunctive treatment in 75 patients with treatment-resistant bipolar (I and II) depression over 24 weeks (Berk et al., 2008). Patients receiving NAC displayed significantly greater improvement in depressive symptoms by 8 weeks of treatment. There were no significant differences among the two treatment groups in adverse events. This intriguing proof-of-concept trial requires replication.

A two-week, crossover randomized controlled trial examined the efficacy of adjunctive ketamine intravenous administration in patients with treatment-resistant bipolar depression (Diazgranados et al., 2010). Patients receiving ketamine during the active phase of the crossover trial displayed a rapid (within 40 minutes) and substantial antidepressant response, with improvement remaining significant, compared with placebo at day 3 after the infusion. Ketamine is an inhibitor of the NMDA-type glutamate channel that has generated a great deal of excitement in depression treatment studies because it appears to reduce depression symptoms almost immediately. Extensive studies of ketamine in the treatment of depression are under way.

Nahas, Kozel, Li, Anderson, and George (2003) compared daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) for 2 weeks with sham rTMS in 23 depressed patients with bipolar I ($N = 12$) or bipolar II ($N = 9$) disorder. No manic switches were observed, but there were also no significant differences in responder rates between the two groups. A trend in favor of mean improvement in depressive symptoms in the active rTMS group may have been significant with a larger sample size.

In a 6-week, placebo-controlled trial, the anticonvulsant levetiracetam was comparable to placebo as adjunctive treatment in 32 patients with bipolar depression (Saricicek et al., 2011).

MAINTENANCE PSYCHOPHARMACOLOGICAL TREATMENT

Lithium

During the late 1960s and 1970s, 10 double-blind, placebo-controlled studies involving 514 patients with bipolar disorder demonstrated that lithium was superior to placebo in preventing recurrent affective episodes (Hopkins & Gelenberg, 1994). The average relapse rate over 1 year was 34% for lithium-treated

patients compared with 81% for those receiving placebo. These data also revealed that lithium exerted greater efficacy in preventing mania than in preventing depressive episodes. Of these 10 studies, 4 were discontinuation trials (Keck et al., 2000a, 2000b; Maj, 2000). Because abrupt discontinuation of lithium appears to precipitate relapse (Baldessarini et al., 1996), this design may have artificially elevated the recurrence rate in patients receiving placebo. Geddes, Burgess, Hawton, Jamison, and Goodwin (2004) conducted a systematic review and meta-analysis of randomized controlled trials comparing lithium and placebo in the long-term treatment of bipolar disorders as part of the Cochrane Collaboration. They identified five randomized controlled trials involving 770 patients. Lithium was more effective than placebo in preventing all relapses (random effects relative risk = 0.65, 95% CI = 0.50 to 0.84) and manic relapses (relative risk = 0.62, 95% CI 0.40 to 0.95). However, the protective effect of lithium on depressive relapses was smaller and less substantial (relative risk = 0.72, 95% CI 0.49 to 1.07). Subsequent naturalistic treatment studies of patients maintained on lithium for more than 1 year indicate that a substantial number of patients do not respond adequately to lithium prophylaxis and that complete prevention of mood episode recurrence is a relatively rare outcome (Baldessarini, Tondo, & Hennen, 2002; Maj, 2000).

Analyses of suicide risk in patients treated with lithium suggest that lithium may exert a specific long-term preventive effect on suicide (Baldessarini, Tondo, & Hennen, 2003b). This risk reduction appears to exceed that predicted by the effects of no treatment and of treatment with divalproex (Goodwin et al., 2003; Tondo, Hennen, & Baldessarini, 2001). Nevertheless, this apparent benefit has not been definitively established in a large, prospective treatment trial controlling for a number of potential confounding effects.

Identification of clinical predictors of response to lithium prophylaxis has been an important area of inquiry over the past several decades. Predictors of favorable response to lithium prophylaxis include a family history of bipolar disorder (Mander, 1986; Mendlewicz, Fieve, & Stallone, 1973; Prien, Caffey, & Klett, 1974), a family history of lithium response (P. Grof et al., 2002), and an illness course characterized by a mania–depression–euthymia episode sequence (Faedda, Baldessarini, Tohen, Strakowski, & Waternaux, 1991; E. Grof et al., 1987; Haag et al., 1986; Koukopoulos et al., 1980). Conversely, predictors of poor maintenance efficacy include rapid cycling (Dunner, Fleiss, & Fieve, 1976), multiple prior episodes (Swann et al., 1999), co-occurring anxiety or alcohol or substance use disorder (Feske et al., 2000; Himmelhoch, Neil, & May, 1980), and familial negative affective style (Miklowitz, Goldstein, Neuechterlein, Snyder, & Mintz, 1988; Miklowitz et al., 2000). With other choices for maintenance treatment becoming available, assessment for these predictors is becoming increasingly important (Keck & Licht, 2000).

In patients successfully treated with lithium prophylaxis, the risks of discontinuing lithium appear to be substantial. For example, in a meta-analysis by Suppes and colleagues (1991) of 14 studies involving a total of 257 bipolar patients who discontinued lithium, the risk of recurrence was approximately 28 times higher per month without medication than with medication. More than 50% of patients who discontinued successful maintenance treatment experienced a relapse (more often of mania than of depression) within 6 months. Other studies found that the risk of recurrence is significantly lower if lithium is discontinued gradually (Baldessarini et al., 1996).

The optimal lithium serum concentration is also directly relevant to successful lithium prophylaxis. Gelenberg and colleagues (1989) found that the risk of relapse was 2.6 times higher in bipolar patients randomized to low (0.4 to 0.6 mol/L) serum concentrations than those with standard (0.8 to 1.0 mol/L) levels. However, patients treated with standard concentrations experienced significantly more side effects. In a second analysis of data from this study, Keller and colleagues (1992) found that patients randomly assigned to the lower range of lithium levels were more likely to experience subsyndromal symptoms, and that their symptoms were more likely to worsen at any time than were the symptoms of patients in the standard-level group. Furthermore, the first occurrence of subsyndromal symptoms increased the risk of full-episode relapse fourfold. Perlis and colleague (2002) also reanalyzed data from the original study and found that patients who had a drop in lithium levels, either due to random assignment to the lower level group or during the trial, were most likely to relapse, and that this was the most powerful predictor of relapse. Finally, in a review of all studies examining maintenance treatment with lithium and lithium serum levels, Hopkins and Gelenberg (2000)

concluded that therapeutic response is correlated with lithium concentration within the range of 0.6 to 1.2 mol/L, as are side effects. Taken together, these studies suggest that lithium should be optimally titrated to the highest level within the therapeutic range consistent with adequate tolerability and that eradication of subsyndromal symptoms, not just prevention of full affective episodes, is an important treatment goal.

Lamotrigine

Lamotrigine was the second medication, after lithium, to receive approval for the long-term treatment of bipolar disorder by the FDA. This indication was based on the results of two 18-month, placebo-controlled lithium comparison studies in which patients entered the trials following stabilization of an acute hypomanic or manic (Bowden et al., 2003) or depressive (Calabrese et al., 2003a) episode, respectively. These designs were chosen because of data suggesting that prior mood episode predicts subsequent episode polarity in relapse (Calabrese et al., 2004; MacQueen et al., 2002). In the study by Bowden and colleagues (2003), patients were randomized to lamotrigine (100 to 400 mg/day), lithium (0.8 to 1.1 mEq/L), or placebo as double-blind maintenance treatment for up to 18 months following an 8- to 16-week open-label phase during which treatment with lamotrigine was initiated and other psychotropics were discontinued. Of 349 patients who entered the open-label phase, 175 met stabilization criteria and entered the randomization phase. Both lamotrigine and lithium were superior to placebo in prolonging the time to intervention for any mood episode. Lamotrigine, but not lithium, was superior to placebo in prolonging time to a depressive episode, whereas lithium, but not lamotrigine, was superior to placebo in prolonging time to a manic, hypomanic, or mixed episode. The second study (Calabrese et al., 2003a) was of similar design, except that there were three fixed-dosage lamotrigine groups (50, 200, or 400 mg/day). The findings of this study were entirely consistent with the results of the study by Bowden and colleagues (2003) and with an earlier 1-year open-label continuation study (McElroy et al., 2004b).

Lamotrigine was compared with placebo in the only published randomized, controlled parallel-group trial conducted specifically in patients with rapid-cycling bipolar I and II disorders (Calabrese et al., 2000). There was no significant difference in efficacy between lamotrigine and placebo in time to additional pharmacotherapy for emerging symptoms, the primary outcome measure in this 6-month trial involving 324 patients. However, significantly more patients remained stable on lamotrigine (41%) compared with placebo (26%) at the end of 6 months. Although not statistically significant, there was a trend toward better response in patients with bipolar II compared with bipolar I disorder.

Olanzapine

Olanzapine has also received an indication for relapse prevention in patients with bipolar disorder. Three randomized controlled trials evaluated the efficacy of olanzapine monotherapy in the long-term prevention of mood episodes in patients with bipolar disorder (Tohen et al., 2003b, 2005, 2006). The first long-term study was a 47-week maintenance of effect comparison with divalproex in patients who had initially responded to either agent for acute mania (Tohen et al., 2003b). The median times to manic relapse were 270 days for the olanzapine group and 74 days for the divalproex group. These differences were not significant. There were also no significant differences in relapse rates between the olanzapine (45%) and divalproex (52%) groups. The second long-term trial was a relapse-prevention study comparing olanzapine with lithium in 543 patients with bipolar I disorder who were initially stabilized on the combination of the two agents following a manic or mixed episode for 6 to 12 weeks (Tohen et al., 2005). Of the initial 543 patients, 431 met symptomatic remission criteria and were randomized to olanzapine (5 to 20 mg/day) or lithium (0.6 to 1.2 mEq/L) for up to 1 year. Significantly more olanzapine-treated patients (47%) completed the trial than lithium-treated (33%) patients. Although there were no significant differences in overall relapse rates into a mood episode between the olanzapine (30%) and lithium (39%) groups, patients receiving olanzapine had significantly fewer manic relapses (14%) compared with patients receiving lithium (28%). Relapse rates into depression were similar for the olanzapine (16%) and lithium (15%) groups. Tohen and colleagues (2006) also conducted a 48-week placebo-controlled trial of olanzapine monotherapy in relapse prevention of bipolar I disorder. Patients

who met criteria for symptomatic remission from a manic or mixed episode at two consecutive weekly visits following 6 to 12 weeks of open-label treatment with olanzapine (5 to 20 mg/day) were randomized to olanzapine (N = 225) or placebo (N = 136) for up to 48 weeks. Patients receiving olanzapine had a significantly longer time to symptomatic relapse (median 174 days) compared with patients receiving placebo (median 22 days). Time to symptomatic recurrence of manic, mixed, and depressive episodes was also significantly longer in the olanzapine group. The overall relapse rates for olanzapine-treated patients were significantly lower (47%) compared with patients receiving placebo (80%). The findings from these trials indicate that olanzapine has efficacy in relapse prevention in patients with bipolar I disorder and suggest that it may be superior to lithium in preventing manic recurrence. Long-term treatment with olanzapine may be associated with significant weight gain, however.

Aripiprazole

The efficacy of aripiprazole in relapse prevention in recently (less than 3 months) manic patients with bipolar I disorder was examined in one 6-month, placebo-controlled trial (Keck et al., 2006a). A total of 633 patients enrolled in the trial; 567 entered the stabilization phase and received aripiprazole 15 or 30 mg/day, of whom 206 (37%) completed. A total of 161 patients entered the 6-month randomization phase after meeting stabilization criteria, which included symptomatic remission for at least 6 weeks on aripiprazole monotherapy. Aripiprazole was superior to placebo in delaying time to relapse into any mood episode and in percentage relapses (aripiprazole, 25%; placebo, 43%). Within mood episodes, aripiprazole was superior to placebo primarily in the prevention of manic or mixed episodes, probably because most of the patients enrolled had been recently manic or mixed.

Three studies examined the efficacy of aripiprazole compared with placebo as adjunctive therapy in the long-term treatment of patients with bipolar I disorder recovering from an acute manic or mixed episode (Carlson et al., 2012; Marcus et al., 2011; Woo et al., 2011). Aripiprazole or placebo was added to lithium or valproate in two studies (Marcus et al., 2011; Woo et al., 2011) and to lamotrigine in one study (Carlson et al., 2012). Aripiprazole displayed significantly greater efficacy in delaying time to relapse to any mood episode in only one of these three trials, when added to lithium or valproate (Marcus et al., 2011).

Quetiapine

In the first of two quetiapine adjunctive maintenance trials (Vieta et al., 2008a), patients received open-label quetiapine (400 to 800 mg/day, flexible, divided doses) in combination with lithium or divalproex at therapeutic plasma concentrations for up to 36 weeks in order to achieve at least 12 weeks of clinical stability. After this 12-week stabilization period, patients were randomized to receive quetiapine or placebo in combination with lithium or divalproex for up to 104 weeks. The combination treatment group had significantly greater time to recurrence of any mood event and a smaller proportion of patients experiencing a mood event compared with the placebo–lithium or placebo–divalproex group. The second quetiapine trial (Suppes et al., 2009), was nearly identical in design, and the adjunctive quetiapine group again displayed significantly longer time to any mood event and risk reductions in mood events, mania, and depression.

In a monotherapy trial (Weisler et al., 2011), continuation of quetiapine among quetiapine responders was superior to placebo and comparable to lithium in patients randomized among the three treatment groups.

Ziprasidone

Ziprasidone (80 to 160 mg/day) was compared with placebo as adjunctive treatment to lithium and valproate following an 8-week period of mood stability on therapeutic levels of lithium or valproate (Bowden et al., 2010). Patients were then randomized to ziprasidone or placebo for 6 months. Patients in the ziprasidone combination group had significantly longer times to intervention for a mood episode and significantly lower rates of intervention for a mood episode compared with the placebo–lithium or placebo–valproate group. In addition, the time to discontinuation was significantly longer for the ziprasidone group.

Risperidone (Long-Acting) and Extended-Release Paliperidone

The efficacy and safety of risperidone long-acting injectable (RLAI) for preventing recurrent mood

episodes in patients with bipolar I disorder was examined in three randomized, placebo-controlled trials (Macfadden et al., 2009; Quiroz et al., 2010; Vieta et al., 2012). The first study randomized patients with a history of at least four mood episodes in the past 12 months, and after 16 weeks of mood stability on RLAI and treatment-as-usual medications for bipolar I disorder, to a 52-week blinded study phase of randomization to RLAI plus treatment as usual or placebo plus treatment as usual (Macfadden et al., 2009). Time to relapse was significantly longer in the group randomized to RLAI. In the second study, patients with bipolar I disorder with a current or recent manic episode were treated with open-label oral risperidone for 3 weeks, and open-label RLAI for 26 weeks (Quiroz et al., 2010). Patients who maintained response were then randomized to placebo injection or to continue RLAI. Time to recurrence for any mood episode was significantly longer in the RLAI group, with time to recurrence significant for a manic but not depressive episode compared with placebo.

In the third trial, after a 12-week open-label period of treatment with RLAI, patients with bipolar I disorder who did not experience a recurrence entered into an 18-month randomized, double-blind treatment arm consisting of RLAI, placebo injection, or oral olanzapine 10 mg/day (Vieta et al., 2012). Time to recurrence of any mood episode was significantly longer in the RLAI group compared with placebo injection, again with the significant difference driven mainly by prevention of manic compared with depressive recurrence. However, RLAI demonstrated less efficacy compared with olanzapine in preventing relapse.

In a 3-month continuation, placebo- and olanzapine-controlled trial, continued extended-release paliperidone had significantly greater efficacy compared with placebo in preventing relapse in prior paliperidone responders treated for acute mania (Berwaerts et al., 2012). However, olanzapine had greater efficacy than paliperidone.

Carbamazepine

Nine controlled studies have assessed the efficacy of carbamazepine for the maintenance treatment of patients with bipolar disorder (Bellaire, Demish, & Stoll, 1988; Coxhead, Silverstone, & Cookson, 1992; Denicoff et al., 1997; Greil et al., 1997; Hartong et al., 2003; Lusznat, Murphy, & Nunn, 1988; Okuma et al., 1981; Placidi et al., 1986; Watkins, Callendar, & Thomas, 1987). However, the efficacy of carbamazepine in the prevention of mood episodes has been controversial (Dardennes, Even, Bange, & Heim, 1995; Murphy, Gannon, & McGennis, 1989). This controversy stems in part from the heterogeneity in design, sample size, liberal use of rescue medications, and other factors affecting trial outcomes among the controlled maintenance studies, and the availability of only one placebo-controlled maintenance trial (Okuma et al., 1981). Interpretation of this latter study is further limited by the use of rescue medications other than lithium or carbamazepine to treat breakthrough symptoms. The use of these adjunctive medications limits the degree to which relapse rates can be directly attributable to carbamazepine or placebo in this study.

Hartong and colleagues (2003) conducted one of the most rigorous trials of carbamazepine prophylaxis in treatment-naïve patients with bipolar I disorder. Patients ($N = 94$) with at least two prior mood episodes in the previous 3 years were randomly assigned to receive lithium or carbamazepine using a double-dummy parallel-group design beginning with an index episode of hypomania, mania, or depression and followed for up to 2 years. No adjunctive thymoleptic medications were allowed. Fewer patients receiving lithium (27%) developed a mood episode compared with patients receiving carbamazepine (42%). Most relapses in the lithium group occurred within the first 3 months of the trial, whereas the relapse rate in the carbamazepine group was approximately 40% per year. However, slightly more patients treated with lithium (36%) than carbamazepine (26%) dropped out of the study, yielding 36% of lithium-treated patients completing 2 years with no episodes compared with 32% on carbamazepine.

Valproate

A 1-year randomized, double-blind, placebo-controlled, lithium-comparator trial of divalproex by Bowden and colleagues (2000) did not find a significant difference in time to any mood episode among the three groups. A post hoc survival analysis that included both time to any mood episode and time to early discontinuation for any reason as

treatment failure events found that patients in the divalproex group had significantly longer time in study compared with the lithium group (Bowden, 2003). The more substantial benefits in relapse prevention for divalproex and lithium were for mania rather than depression (Bowden, 2003). In contrast, time to depression was longer and the need for rescue intervention with antidepressants was significantly less in the divalproex group compared with the lithium and placebo groups (Gyulai et al., 2003).

Revicki and colleagues (2005) conducted an open-label one-year study of the clinical effectiveness (efficacy and tolerability) of divalproex compared with lithium in 201 patients with bipolar I disorder randomized to either drug initially for the treatment of an acute manic or mixed episode requiring hospitalization. Divalproex-treated patients (12%) were less likely to discontinue study medications for lack of efficacy or adverse events compared with lithium-treated patients (23%). No other significant differences in clinical outcome measures were evident between the two groups.

Combination Therapy

The efficacy of mood stabilizer combinations compared with mood stabilizer monotherapy is a remarkably understudied aspect of the long-term treatment of bipolar disorders. Only two such prospective randomized double-blind trials have been reported: a 1-year pilot trial comparing the combination of lithium and divalproex with lithium and placebo (Solomon et al., 1997), and a large 18-month trial comparing the combination of olanzapine with lithium or divalproex versus placebo with lithium or divalproex (Tohen et al., 2004). Solomon and colleagues (1997) found lower relapse rates in patients receiving divalproex and lithium ($N = 5$) compared with patients receiving placebo and lithium ($N = 7$) but higher rates of side effects in the combination treatment group. Tohen and colleagues (2004) reported significantly lower relapse rates in patients receiving combination olanzapine with lithium or divalproex compared with placebo plus lithium or divalproex. The greatest protective effect in the combination group was in the prevention of manic relapse. Again, not surprisingly, side effects, in particular weight gain, were more common in the combination group. The results of this study need to be considered in light of the original cohort selection, which was based on patients who were partial nonresponders to monotherapy with lithium or divalproex after 2 weeks of treatment for manic or mixed symptoms (Tohen et al., 2002b).

The Bipolar Affective Disorder Lithium/Anticonvulsant Evaluation (BALANCE) Study was a 2-year, open-label comparison of the long-term efficacy of lithium monotherapy, divalproex monotherapy, and the combination following an initial treatment period with the combination (Geddes et al., 2010). Both the combination and lithium monotherapy were superior to divalproex monotherapy in preventing relapse. Interpretation of the results of this study must be considered in light of the fact that the patients were discontinued from combination therapy before randomization and the open-label design.

Three large naturalistic studies found the combination of lithium and carbamazepine superior to lithium monotherapy in preventing bipolar disorder relapse, although these studies were enriched for carbamazepine responders, and the side effect burden was not unexpectedly greater in the combination therapy groups (Baethge et al., 2005; Bocchetta, Chillotti, Severino, Ardau, & Del Zompo, 1997; Denicoff et al., 1997).

Two studies addressed the impact of antipsychotic discontinuation on relapse in patients initially treated with the combination of an antipsychotic (usually an FGA) and an antimanic mood stabilizer for acute mania (Saksa, Baker, & Woods, 2004; Zarate & Tohen, 2004c). Zarate and Tohen (2004c) randomized 37 patients receiving perphenazine in combination with lithium, carbamazepine, or valproate to remain on perphenazine or switch to placebo for 6 months immediately after remission of an acute manic episode for which they received both agents. Patients who continued on the combination of perphenazine and mood stabilizer were significantly more likely to have a shorter time to depressive relapse, to discontinue the study, and to have increased rates of dysphoria, depressive symptoms, and extrapyramidal symptoms. The study by Saksa and colleagues (2004) was limited by a high dropout rate, but two of five patients randomized to discontinue adjunctive antipsychotic therapy relapsed into psychotic and manic recurrence, respectively, within 1 month of the antipsychotic taper.

CO-OCCURRING PSYCHIATRIC DISORDERS

Patients with bipolar disorders have among the highest rates of psychiatric comorbidity of all primary psychiatric illnesses (McElroy et al., 2001). The presence of co-occurring psychiatric disorders can affect treatment selection. Unfortunately, very few studies have specifically addressed the long-term treatment of patients with bipolar disorder and psychiatric comorbidity. Frankenburg and Zanarini (2002) conducted a 6-month placebo-controlled trial of divalproex in 30 female patients with bipolar II disorder and co-occurring borderline personality disorder. Divalproex was superior to placebo in reducing measures of interpersonal sensitivity, anger, hostility, and aggression. In an 8-week, placebo-controlled trial of outpatients with bipolar disorder and co-occurring generalized anxiety disorder or panic disorder, patients treated with risperidone did not display improvement in measures of anxiety symptoms compared with placebo (Sheehan et al., 2009).

Salloum and colleagues (2005) conducted a 24-week, double-blind, placebo-controlled trial of adjunctive divalproex or placebo in 59 patients with bipolar I disorder and co-occurring alcohol dependence receiving lithium and psychosocial treatment. Patients receiving divalproex had a significantly lower proportion of heavy drinking days and a trend toward fewer drinks per heavy drinking day compared with patients receiving placebo. Higher serum valproic acid concentrations correlated with better alcohol use outcomes. There were no significant differences between the two groups in mood symptom improvement. In two related studies, adjunctive quetiapine was compared with placebo in reducing heavy drinking days in a 12-week study of patients with bipolar I disorder and alcohol dependence who were also receiving lithium or divalproex at therapeutic concentrations (Brown et al., 2008; Stedman et al., 2010). There were no significant differences between the two treatment groups in reduction of heavy drinking days or in secondary measures of first two consecutive weeks of abstinence, changes in proportion of nondrinking days, or other measures. Kemp and colleagues (2009) conducted a 6-month randomized controlled trial comparing the combination of lithium and divalproex with lithium monotherapy among patients with bipolar disorder, recently manic and rapid cycling with co-occurring substance use disorder who initially responded to combination therapy. Only 31 of 149 patients who entered the open-label phase of this study were subsequently randomized, and of these 55% relapsed, with no significant differences between treatment groups. These findings are limited by the small sample size of patients who entered the randomized phase of the trial. This group (Wang et al., 2010) conducted a similar trial of lamotrigine compared with placebo as adjunctive therapy to lithium for 12 weeks in patients with rapid-cycling bipolar disorder and co-occurring substance use disorder. Only 8 patients per treatment arm completed the trial.

The treatment of bipolar disorder and co-occurring stimulant use disorders has been studied in two randomized clinical trials to date (Brown et al., 2007; Nejtek et al., 2008). In the only placebo-controlled trial, a 12-week study involving 44 patients with bipolar I or II disorder and co-occurring cocaine dependence, citicoline, an over-the-counter psychostimulant, added to ongoing mood stabilizer treatment, significantly improved some aspects of declarative memory and cocaine use, but not mood compared with placebo (Brown et al., 2007). Nejtek and colleagues (2008) randomized 80 patients with bipolar disorder and co-occurring cocaine or methamphetamine dependence to treatment with quetiapine or risperidone for 20 weeks. Both treatment groups displayed improvement in manic and depressive symptoms, as well as drug craving and use, with no significant difference between groups. This study did not include a placebo arm and the sample size was likely too small to detect potential treatment differences.

FUTURE RESEARCH AND CONCLUSIONS

There have been substantial advances in the pharmacological treatment of bipolar disorder in the past two decades. Well-done randomized controlled trials have established the efficacy of lithium, divalproex, carbamazepine, chlorpromazine, haloperidol, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and asenapine in the treatment of acute mania. Research into neglected but important aspects of the management of bipolar disorder—the treatment of acute bipolar depression and the long-term prevention of relapse—has finally gained momentum. Four agents have FDA indications for relapse prevention of bipolar I disorder: lithium, lamotrigine, olanzapine, and aripiprazole. Studies of the efficacy of quetiapine and

ziprasidone in the long-term treatment of bipolar disorder are under way. Although only one formulation, the combination of olanzapine and fluoxetine, has an indication for acute bipolar depression, evidence is beginning to emerge that some other agents, most notably quetiapine and lamotrigine, may also be efficacious in this pole of the illness without increasing the risk of hypomanic or manic switch. Recent studies have also shed light on the lack of efficacy of some agents initially hypothesized to have potential in the treatment of bipolar disorder, for example gabapentin and topiramate. The thymoleptic properties of the anticonvulsants levetiracetam, oxcarbazepine, and zonisamide require careful delineation in randomized controlled trials.

Important therapeutic questions remain unanswered. For example, the optimal duration of antidepressant treatment in combination with antimanic mood stabilizers, balanced against the risk of switch induction, is unclear from the available research. Very few data exist regarding the efficacy and effectiveness of long-term treatment of bipolar disorder with combinations of mood-stabilizing agents, even though this is common practice. Entirely novel treatment approaches such as tamoxifen, allopurinol, NAC, and rTMS have not been adequately explored in patients with bipolar disorder. Moreover, studies of patients with bipolar disorder and co-occurring illnesses have only just begun.

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The following coding system, with codes provided at the end of each reference entry, indicates the nature of the supporting evidence from each citation:

1. Randomized, prospective, clinical trial. A study must include comparison groups with random assignment, blinded assessments, clear presentation of inclusion and exclusion criteria, state-of-the-art diagnostic methods, adequate sample size to provide statistical power, and clearly described statistical methods.

2. Clinical trial. A study in which an intervention is made but some aspect of the type 1 study criteria is missing.

3. Clinical study. A study that has clear methodological limitations. These studies include open treatment studies designed to obtain pilot data, naturalistic studies, and case-control studies.

4. A review with secondary data analysis (e.g., meta-analysis or comparably designed trials).

5. A review without secondary data analysis designed to convey an impression of the available literature.

6. A textbook, reference manual, case reports, small case series, and opinion papers.

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9

Treatments for Pediatric Bipolar Disorder

Pablo H. Goldberg
Prerna Martin
Carolina Biernacki
Moira A. Rynn

The past two decades have seen significant advances in the development of evidence-based treatments for pediatric bipolar disorder (PBD). Practice guidelines recommend pharmacotherapy with mood stabilizers or second-generation antipsychotics (SGAs) as the first-line treatment for PBD. Currently, lithium, risperidone, aripiprazole, quetiapine, and olanzapine are approved by the U.S. Food & Drug Administration (FDA) for treating bipolar disorder in children and adolescents. The pharmacological literature suggests that SGAs are faster and more effective than mood stabilizers in treating acute manic or mixed episodes; however, they have significant side effects and require careful monitoring. While mild to moderate PBD can be treated with monotherapy, combination pharmacotherapy with an SGA and a mood stabilizer is recommended for youth with severe PBD. A growing body of literature also suggests the efficacy of psychosocial interventions with family psychoeducation and skills building as adjunct treatments to pharmacotherapy. More type 1 studies for both pharmacotherapy and psychosocial treatments are needed to better inform treatment recommendations.

BACKGROUND

PBD is a chronic, disabling illness characterized by significant symptoms, comorbidity, recurrence, and suicide risk leading to serious disruption in the lives of children and adolescents affected by it (Birmaher et al., 2009). The symptoms of PBD include but are not limited to disturbance in mood, poor judgment, grandiosity, aggressive behaviors, sleeplessness, hypersexual behavior, racing thoughts, and pressured speech. Children and adolescents with PBD often underperform academically, are disruptive in school, and have neurocognitive deficits (Henin et al., 2007; Pavuluri et al., 2006b). They may have poor social skills and social networks and experience frequent victimization by their peers (Geller et al., 2002; Goldstein et al., 2006). Within families, they experience significant conflict with parents and siblings, lower levels of family cohesion, and increased chronic stress (Geller et al., 2000; Kim et al., 2007; Wilens et al., 2003). Interpersonally, youth with PBD also demonstrate low self-esteem, hopelessness, and poor coping skills (Rucklidge, 2006). Bipolar disorder seems to be more severe in children and adolescents than adults in terms of morbidity, mortality, and affected quality of life (Freeman et al., 2009), thus carrying a poorer prognosis (Leverich et al., 2007). The description of PBD has been in existence for a century (Carlson & Glovinsky, 2009; Kraepelin, 1921), but research on PBD and its treatment has become more rigorous in the past 15 to 20 years. There has also been a forty-fold increase in the diagnosis of PBD between

1994 and 2003. PBD has likely been underdiagnosed in the past due to poor conceptualization of the disorder, including lack of age-specific and clear diagnostic criteria, low concordance across informants, and diagnostic uncertainty related to high comorbidity of attention-deficit/hyperactivity disorder (ADHD) in the pediatric population (Moreno et al., 2007).

EPIDEMIOLOGY AND RISK

Lifetime prevalence of adult bipolar disorder (BD) has been reported to be 3.9% (Perlis et al., 2004). The prevalence of PBD has not been well studied, perhaps due to its complex presentation in this population. There have been more reports of comorbidity in PBD than in adults with BD: 32% of youth with PBD have comorbidities compared to 3% in adults (Moreno et al., 2007). The first epidemiological data on PBD appeared in the Epidemiological Catchment Area Study (0.8% to 1.4% depending on the city, 1980–1985) (Robins & Price, 1991). In the 1990 National Comorbidity Survey (Kessler et al., 1994) the rate of BD appeared to be slightly lower in adolescents aged 15 to 17 (1.3%) compared to the full sample (1.7%) (Merikangas et al., 2010). Rates of PBD have also varied by country, from 0.3% to 1.7% (Merikangas et al., 2010; Weissman et al., 1996). According to the National Institute of Mental Health's Methods for the Epidemiology of Child and Adolescent Disorders (MECA) Study, the six-month prevalence was 1.6% for mania and 0.6% for hypomania in a population-based sample of children and adolescents (Lahey et al., 1996). In the biggest sample to date, Lewinsohn, Klein, and Seeley (1995) determined that BD (primarily bipolar II disorder and cyclothymia) had a lifetime prevalence of 1% in older adolescents ($N = 1{,}709$, aged 14 to 18 years) from nine senior high schools representing rural and urban districts of western Oregon. The risk factors for PBD include lifetime history of mood disorders, history of BD in the family (Hodgins et al., 2002), antidepressant-induced mania, episodic mood lability, early-onset depression, presence of psychosis, and episodic aggressive behavior (Youngstrom et al., 2009).

DIAGNOSTIC CRITERIA

There has been considerable debate regarding how BD is conceptualized in children and adolescents. This could be due to the developmental differences in phenomenology of this illness and/or overlap with other conditions that present with similar symptoms, such as ADHD, oppositional-defiant disorder, and conduct disorder. There has been ongoing controversy as to whether the diagnosis of PBD should be confined to patients who have discrete episodes of mania and depression versus patients who have a more chronic emotional dysregulation (Carlson & Glovinsky, 2009). The National Institute of Mental Health research roundtable on prepubertal BD proposed the classification of PBD in "narrow" or "broad" phenotypes (Nottelmann, 2001). Patients with narrow phenotypes fit the classic definition of bipolar I disorder (BD I) and bipolar II disorder (BD II) described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*; American Psychiatric Association [APA], 1994). In contrast, those with the broad phenotype present with severe irritability, affective storms, mood lability, severe temper outbursts, symptoms of depression, anxiety, hyperactivity, poor concentration, and impulsivity without clear episodicity. Due to the controversies about symptomatology, duration, and comorbidity in children, Leibenluft and colleagues (2003) proposed three main phenotypes of PBD: *narrow phenotype* (with the mania definition adjusted to fit the *DSM* definition and the hallmark symptoms of grandiosity or elevated mood); *broad phenotype* (chronic, nonepisodic symptoms of severe irritability and hyperarousal, without the hallmark symptoms of elevated mood and grandiosity); and *intermediate phenotype*, with two subcategories: (hypo)mania not otherwise specified (1 to 3 days in duration) and irritable (hypo)mania (fitting the BD not otherwise specified symptoms).

Defining the Disorder

According to the *DSM-5* (APA, 2013), a diagnosis of BD I requires the presence of a manic episode that may be preceded or followed by a hypomanic or major depressive episode. The diagnosis of BD II requires the presence of at least one major depressive episode and a hypomanic episode. A cyclothymia diagnosis is given to children who experience a full year of both hypomanic and depressive periods but do not meet full criteria for a hypomanic or major depressive episode. The *DSM-5* also includes a group of bipolar and related disorders that are induced by substances

or medications or occur due to a medical condition. The classic symptoms of mania in BD include grandiosity, insomnia, pressured speech, racing thoughts, inattention, and increase in goal-directed activity (e.g., hypersexuality). To meet criteria for a manic episode, patients must have at least three symptoms (four if the mood is only irritable) lasting at least a week, nearly every day (or for any duration if the patient is hospitalized). In hypomania, the same symptoms last for at least four consecutive days (APA, 2013). The presentation of BD in children seems to differ when compared to adults, as children often present with nonepisodic chronic irritability, aggression, mood lability, and impulsive behaviors, which may last from a few hours to a few days. There seems to be much more cycling in children than in adults (Geller et al., 2000).

Special considerations are necessary when making the diagnosis of PBD. Since children of the same chronological age may be at different developmental stages, it is difficult to define with precision what is "normal" or "expected" at any given point. Therefore, each child should be assessed according to his or her own baseline of functioning and symptom presentation. The age of onset of PBD remains controversial. If the broad phenotype is considered, then the condition is understood to start as early as during preschool (Carlson & Meyer, 2010). Considering all bipolar disorders, at least half of the cases start before age 25 (Kessler et al., 2005). Despite these controversies, the validity of the *DSM-IV* and *DSM-5* diagnoses has been supported by substantial evidence (APA, 2000, 2013).

Depressive symptoms are common in youth with BD. The criteria for having a major depressive episode remain mostly the same in the *DSM-5* and consist of depressed mood and/or loss of interest or pleasure in life activities for at least 2 weeks, along with five or more of the following symptoms causing significant impairment in functioning: (1) depressed mood (or irritability in children and adolescents), (2) marked diminished interest or pleasure in daily activities, (3) significant weight loss, weight gain, or decrease or increase in appetite, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feelings of worthlessness or guilt, (8) decreased concentration or indecisiveness, and (9) recurrent thoughts of death or suicide (APA, 2013). More than 50% of youth with BD I have had a prior history of a major depressive episode (Axelson et al., 2006). Psychotic symptoms are present in 16% to 60% of children and adolescents with BD, with auditory hallucinations being the most common (Pavuluri et al., 2005). To enhance the accuracy of diagnosis and facilitate earlier detection in clinical settings, the criteria for manic and hypomanic episodes now include an emphasis on changes in activity and energy as well as mood. The *DSM-IV* diagnosis of BD I, mixed episode, requiring that the individual simultaneously meet full criteria for both mania and major depressive episode, has been removed. Instead, a new specifier, "with mixed features," has been added, which can be applied to BD when depressive features are present or to major depressive disorder with manic or hypomanic features.

DSM-5 allows the specification of particular conditions for "other specified bipolar and related disorders," including categorization for individuals with a past history of major depressive disorder who meet all criteria for hypomania except the duration criterion (i.e., at least four consecutive days). A second condition that is conceptualized within this category occurs when too few symptoms of hypomania are present to meet criteria for the full bipolar II syndrome, although the duration is sufficient at four or more days. Other conditions in this category include hypomania alone without major depression and short-duration cyclothymia (less than 24 months). The specifier "with anxious distress" has been added to the *DSM-5*, along with rapid cycling, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, catatonia, peripartum onset, and seasonal pattern (APA, 2013). Finally, disruptive mood dysregulation disorder differs from BD in terms of episodicity and should not be included in the PBD diagnosis (APA, 2013).

PHARMACOLOGICAL TREATMENT FOR PEDIATRIC BIPOLAR DISORDER

The two main classes of biological agents used to treat PBD are mood stabilizers and SGAs. Due to the limited number of randomized controlled trials (RCTs) of psychopharmacological treatments of PBD, some open trials and chart reviews have been included judiciously to take into account the past five to six years of research in the field. The fundamental landmark studies are also discussed. In this review, medication trials for PBD are classified based on the following

treatment phases (Hirschfeld et al., 2002; Kowatch et al., 2005). *Acute treatment trials* usually refer to the first 6 to 8 weeks of treatment, during which the goal is to stabilize acute mania symptoms in order to allow the patient to return to his or her baseline level of psychosocial functioning. This section includes monotherapy and combination treatment trials, pediatric bipolar depression trials, and trials for PBD comorbid with other conditions such as ADHD, anxiety, and substance abuse. *Maintenance or continuation treatment trials* refer to treatment that is provided following remission of an acute manic episode. After remission, patients may remain at a particularly high risk of relapse for up to 6 months. This phase of treatment is sometimes referred to as *continuation* treatment and is considered part of the *maintenance* phase. The goals of maintenance treatment include prevention of relapse and recurrence; reduction of subthreshold symptoms, suicide risk, affective cycling, and mood instability; reduction of vocational and social morbidity; and promotion of wellness. The maintenance phase can last up to 24 months. Table 9.1 provides a summary of pharmacological trials for treating PBD, including indications for study type, sample size, and treatment outcomes.

ACUTE TREATMENT FOR MANIC AND MIXED EPISODES

Monotherapy Trials

Mood Stabilizers: Lithium

Lithium was the first drug to be approved by the FDA for the treatment of mania in children 12 years and older; approval followed its success in treating adults. Lithium should be titrated to 30 mg/kg per day in two or three divided dosages (Kowatch et al., 2011). Lithium has a narrow therapeutic index (0.8 to 1.2 mEq/L), and higher dosages are needed to obtain a therapeutic level (Findling et al., 2008a). Lithium's narrow therapeutic range can precipitate significant adverse effects, particularly at toxic levels, as noted by the FDA's black box warning (FDA, 2011). To achieve an accurate lithium level, blood should be drawn 12 hours after a dose. A physical examination should be completed before the start of the lithium treatment, with careful attention to ruling out any renal conditions. Bloodwork should include a lithium level, blood urea nitrogen, creatinine concentration, thyroid function tests, electrolytes, and a complete blood count. This should be repeated every three months once a steady state is achieved, which is usually after 1 week of starting the medication in children. Pregnancy tests should be obtained for adolescents of childbearing age. Education on reliable contraception should be reviewed due to lithium's potential to cause birth defects such as Ebstein's anomaly. Patients should be educated to maintain adequate fluid intake to prevent dehydration. Lithium can lead to significant weight gain and requires careful monitoring. Adverse effects of lithium include nausea, vomiting, diarrhea, hypothyroidism, renal function abnormalities, polyuria, polydipsia, leukocytosis, tremors, and acne. If toxicity occurs, the dose should be either discontinued or lowered. The symptoms of lithium toxicity include loss of balance, increased diarrhea, vomiting, anorexia, weakness, ataxia, blurred vision, tinnitus, polyuria, coarse tremor, muscle twitching, irritability, and agitation. The drugs that can increase lithium levels are carbamazepine, nonsteroidal anti-inflammatories (NSAIDs), tetracycline, and thiazide diuretics. Theophylline and caffeine promote lithium excretion, resulting in lower serum levels at the same oral dose (Findling & Pavuluri, 2008).

There are only two studies in children that have evaluated lithium as a monotherapy with rigor, using a double-blind controlled design for acute treatment of mania or mixed episodes. In 1998, Geller and colleagues randomized 25 patients (aged 12 to 18 years) with comorbid PBD, manic or mixed episode, and secondary substance dependence to receive lithium (0.9 to 1.3 mEq/L) or placebo over a period of six weeks. Results of this trial indicated clinically significant improvement in patients taking lithium, with response rates for lithium (46%) separating from placebo (8%) as measured by a score of 65 or greater on the Children's Global Assessment Scale (CGAS). However, when assessing improvement using the Schedule for Affective Disorders and Schizophrenia for School Aged Children (Puig-Antich & Ryan, 1986), there was no significant difference between active and placebo groups.

The Collaborative Lithium Trials (CoLT) consisted of two multiphase trials (CoLT 1 and CoLT 2) that examined the safety and efficacy of lithium for the treatment of children and adolescents (aged 7 to 17 years) diagnosed with BD I, manic or mixed

TABLE 9.1 Summary of Pharmacologic Trials for Treatment of Bipolar Disorder in Children and Adolescents

Type of Pharmacologic Treatment	*Citation*	*Design/Duration*	*Class Type*	*Sample Size (N)*	*Age Range*	*Results/Outcome Measure*
Acute Treatment for Manic or Mixed Episodes (Monotherapy Trials)						
Li vs. PBO	Geller et al., 1998	RCT 6 weeks	1	25	12–18	Li = PBO (↓YMRS) Li > PBO (↑ CGAS) Response rate 46% (Li), 8% (PBO)
Li vs. DVPX vs. CBZ	Kowatch et al., 2000	Open label 6 weeks	2	42	8–18	Response rate 38% (Li), 53% (DVPX), 38% (CBZ)
DVPX-ER vs. PBO	Wagner et al., 2009	RCT 28 days	1	150	10–17	DVPX-ER = PBO (↓YMRS) Response rate 24% (DVPX-ER), 23% (PBO)
DVPX	Pavuluri et al., 2005	Open label 6 months	3	34	5–18	↓YMRS, ↓CDRS-R Response rate 73.5%, remission 52.9%
Li vs. DVPX vs. PBO	Kowatch et al., 2007	RCT 8 weeks	1	153	7–17	DVPX > PBO, Li = PBO Response rate 54% (DVPX), 42% (Li), 29% (PBO)
CBZ-ER	Joshi et al., 2010	Open label 8 weeks	3	27	6–12	↓YMRS (mean YMRS score at study endpoint 21.8 ± 12.2)
OCBZ vs. PBO	Wagner et al., 2006	RCT 7 weeks	1	116	7–18	OCBZ = PCBO (↓YMRS) Response rate 42% (OCBZ), 26% (PBO)
LTG	Biederman et al., 2010	Open label 12 weeks	3	39	6–17	↓ YMRS & CGI ≤ 2 Response rate 66% (≥12 years), 54% (<12 years)
TPM vs. PBO	DelBello et al., 2005	RCT 4 weeks	2	56	6–17	↓YMRS (Discontinued early)
RIS vs. PBO	Haas et al., 2009	RCT 3 weeks	1	169	10–17	↓YMRS Response rate 59% (RIS, 0.5–2.5 mg), 63% (RIS, 3–6 mg), 26% (PBO)
RIS vs. DVPX	Pavuluri et al., 2010	RCT 6 weeks	2	66	8–18	RIS > DVPX (↓YMRS) Response rate 78.1% (RIS), 45.5% (DVXP) Remission 62.5% (RIS), 33.3% (DVPX)
RIS vs. Li vs. DVPX	Geller et al., 2012	RCT 8 weeks	1	279	6–15	RIS > Li (CGI-BP-IM ≤ 2) RIS > DVPX Li = DVPX Response rate 68.5% (RIS), 35.6% (Li), 24% (DVPX)

(continued)

TABLE 9.1 (continued)

Type of Pharmacologic Treatment	*Citation*	*Design/Duration*	*Class Type*	*Sample Size (N)*	*Age Range*	*Results/Outcome Measure*
QTP vs. PBO	Pathak et al., 2013	RCT 3 weeks	1	284	10–17	QTP > PBO (↓YMRS) Response rate 64% (QTP, 400 mg/day), 58% (QTP, 600 mg/day), 37% (PBO) Remission 45% (QTP 400 mg/day), 52% (QTP 600 mg/day), 23% (PBO)
QTP vs. DVPX	DelBello et al., 2006	RCT 28 days	1	50	12–18	QTP = DVPX (↓YMRS) Response rate 72% (QTP), 40% (DVPX) Remission 60% (QTP), 28% (DVPX)
Arip vs. PBO	Findling et al., 2009	RCT 4 weeks	1	296	8–17	Arip > PBO (↓YMRS) Response rate 44.8% (Arip 10 mg/day), 63.6% (Arip 30 mg/day), 26.1% (PBO) Remission rate 25% (Arip 10 mg/day), 48% (Arip 30 mg/day), 5% (PBO)
Arip vs. PBO	Tramontina et al., 2009	RCT 6 weeks	1	43	8–17	Arip > PBO (↓YMRS) Response rate 88.9% (Arip), 52% (PBO) Remission 72% (Arip), 32% (PBO)
Arip	Findling et al., 2008	Open label Sequential-cohort, dose-escalation study 26 days total	3	21	10–17	↓CGI-S, ↓CGI-I Arip (20, 25. & 30 mg/day) after upward titration from 2 mg/day was safe and well tolerated
Arip	Findling et al., 2011	Open label up to 16 weeks	3	96	4–9	Response rate 62.5% (↓YMRS, (↓CGI-S, ↑CGAS, & ↓CDRS-R)
Arip	Tramontina et al., 2007	Open label 6 weeks	3	10	8–17	↓YMRS
Arip	Gibson et al., 2007	Retrospective chart review	3	45	11–18	Response rate 51% (↓CGI-S)
OLZ vs. PBO	Tohen et al., 2007	RCT 3 weeks	1	161	13–17	OLZ > PBO (↓YMRS) Response rate 48.6% (OLZ), 22.2% (PBO) Remission rate 35.2% (OLZ), 11.1% (PBO)
ZPS	Biederman et al., 2007	Open label 8 weeks	3	21	6–17	↓ YMRS Response rate 57% (CGI-I ≤ 2)
ZPS	DelBello et al., 2008	Open label 27 weeks total	3	63	10–17	↓ YMRS

ZPS vs. PBO	DelBello et al., 2008 (unpublished)	RCT 4 weeks	1	238	10–17	ZIP > PBO (↓YMRS) Response rate 62% (ZIP), 35% (PBO)
CLO	Masi et al., 2002	Open label 15–28 days	3	10	12–17	↓CGI-S, ↓CGI-I, ↓YMRS, ↑CGAS
Acute Treatment for Manic or Mixed Episodes (Combination Trials)						
DVPX + PBO vs. DVPX + QTP	DelBello et al., 2002	RCT 6 weeks	1	30	12–18	DVPX + QTP > DVPX + PBO (↓YMRS) Response rate 87% (DVPX + QTP), 53% (DVPX + PBO)
RIS + Li vs. RIS + DVPX	Pavuluri et al., 2004	Open label 6 months	2	37	5–18	RIS + Li = RIS + DVPX (↓YMRS) Response rate 82.4% (RIS + Li) & 80% (RIS + DVPX)
RIS + Li	Pavuluri et al., 2006a	Open label 12 months	3	38	4–17	Response rate 85.7% (RIS + Li) Remission 57.1% (RIS + Li)
OLZ + TPM vs. OLZ	Wozniack et al., 2009	Open label 8 weeks	2	40	6–17	OLZ + TPM = OLZ (↓YMRS)
Li + DVPX	Findling et al., 2003	Open label 20 weeks	3	90	5–17	↓YMRS, ↓CDRS, ↑CGAS Remission 47%
Li + DVPX	Findling et al., 2006	Open label 8 weeks	3	38	5–17	↓YMRS, ↓CDRS, ↑CGAS, ↓CGI-S Response rate 89.5%
Acute Treatment of Bipolar Depression						
Li	Patel et al., 2006	Open label 6 weeks	3	27	12–18	Response rate 48% Remission 30%
LTG vs. LTG + Li, stimulants, or antipsychotics	Chang et al., 2006	Open label 8 weeks	3	20	12–17	LTG = LTG + adjunctive medication (↓CDRS-R) Response 63% (LTG) Remission 58% (LTG)
QTP vs. PBO	DelBello et al., 2009	RCT 8 weeks	1	32	12–18	QTP = PBO (↓YMRS, ↓CDRS-R, ↓CGI-BP-I)
Maintenance Treatment of PBD						
Li vs. PBO	Kafantaris et al., 2004	RCT 2 weeks	2	40	12–18	Li = PBO (CGI-I); similar rates of symptom exacerbation: 52.6% (Li) vs. 61.9% (PBO)
Li vs. DVPX	Findling et al., 2005	RCT 76 weeks	1	139	5–17	Li = DVPX (time to recurrence of symptoms)

(continued)

TABLE 9.1 (continued)

Type of Pharmacologic Treatment	*Citation*	*Design/Duration*	*Class Type*	*Sample Size (N)*	*Age Range*	*Results/Outcome Measure*
DVPX-ER	Redden et al., 2009	6 months	3	226	9–17	↓YMRS
LTG + SGA	Pavuluri et al., 2009	Open label crossover 14 weeks	3	46	8–18	Response rate 82% (↓YMRS) Response rate 71% (↓CDRS-R) Remission 56%
Arip vs. PBO	Findling et al., 2012	RCT 72 weeks	1	60	4–9	Arip > PBO (time to discontinuation) Arip = PBO (↓CDRS-R, ↓YMRS, ↑CGAS)
Treatment of Comorbid Conditions						
MAS + DVPX vs. DVPX + PBO	Scheffer et al., 2005	RCT crossover 4 weeks	2	30	8–17	DVPX + MAS > DVPX + PBO (↓ADHD symptoms via CGI-I) DVPX + MAS = DVPX + PBO (↓YMRS)
MPH + MS vs. MPH + PBO	Findling et al., 2007	RCT crossover 4 weeks	2	16	5–17	MPH + MS > MPH + PBO (↓ADHD Rating Scale-IV) MPH + MS = MPH + PBO (↓YMRS or ↓CDRS-R)
Arip + MPH vs. Arip + PBO	Zeni et al., 2009	RCT crossover 4 weeks	2	16	8–17	Arip + MPH = Arip + PBO (↓ SNAP-IV, ↓YMRS, ↓CDRS-R)

Arip = aripiprazole; CBZ = carbamazepine; CBZ-ER = carbamazepine extended-release; CLO, clozapine; DVPX, divalproex sodium; DVPX-ER = divalproex sodium extended-release; Li = lithium; LTG = lamotrigine; OCBZ = oxcarbazepine; OLZ = olanzapine; MAS = mixed amphetamine salts; MPH = methylphenidate; MS = mood stabilizer; PBO = placebo; QTP = quetiapine; RCT = randomized controlled trial; RIS = risperidone; SGA = second-generation antipsychotics; TPM = topiramate; ZPS = ziprasidone.

episode. As established in the written request to the FDA, the goals of the studies were to (1) establish evidence-based dosing strategies for lithium; (2) characterize the pharmacokinetics and biodisposition of lithium; (3) examine the acute efficacy of lithium in pediatric bipolarity; (4) investigate the long-term effectiveness of lithium treatment; and (5) characterize the short- and long-term safety of lithium (Findling et al., 2008a). Both CoLT studies provided up to a maximum of 52 weeks of treatment and had four phases: acute treatment, long-term stabilization, discontinuation, and restabilization. The purpose of CoLT 1 was to develop dosing strategies for lithium in children and adolescents with PBD. In CoLT 2, the first phase began with an 8-week double-blind, placebo-controlled trial where 81 subjects were randomized to receive either lithium or placebo. This initial efficacy phase was followed by an open-label long-term phase of either 16 or 24 weeks in duration, depending on the treatment that the patient received during the first double-blind phase. Study participants were eligible to enter phase 2 if they responded partially or fully to lithium, or did not respond fully to placebo. At the end of phase 2, participants who met criteria for remission of psychotic features and mood symptoms (as measured by Young Mania Rating Scale [YMRS] score <10 and the Children's Depression Rating Scale–Revised [CDRS-R] score ≤ 35) and were determined stable entered phase 3 (discontinuation phase), where they were blindly randomized to either continue on their present lithium treatment or gradually switch to placebo over a period of 28 weeks. Finally, participants who relapsed entered phase 4 (restabilization phase) and received 8 weeks of open-label treatment with lithium (Findling et al., 2008a; IRB, personal communication, July 5, 2012). The CoLT 1 and CoLT 2 studies have been completed and the results are being analyzed.

Several open trials have been conducted using lithium to treat pediatric mania, showing improvement in both mania and depression after 4-6 weeks. For example, Kowatch and colleagues (2000) conducted an open-label trial where 42 participants with BD I or BD II, mixed or manic episode (aged 8 to 18 years), were randomized to receive treatment with lithium, divalproex sodium, or carbamazepine for six weeks. The results of this study indicated large effect sizes as defined by Cohen (1998) for all three mood stabilizers (1.06 for lithium, 1.63 for divalproex sodium, and 1.00 for carbamazepine). Response rates, as defined by at least a 50% change from baseline YMRS score, were 38% for lithium, 53% for divalproex sodium, and 38% carbamazepine. There was no significant difference in response rates among the three groups; however, the sample size of this study was not adequate to detect such a difference. There were no serious adverse effects with any of the three mood stabilizers in this trial.

Anticonvulsants

Divalproex SodiumDivalproex sodium is one of the most widely studied anticonvulsants in the treatment of PBD. Divalproex has a narrow therapeutic window; the starting dose is 15 mg/kg per day to be administered in two or three divided dosages in children and adolescents. Optimal serum levels for treating mania in adults are between 85 and 110 μg/mL, and the same is thought to be true for the pediatric population (Kowatch et al., 2011). Common adverse events include weight gain, tremor, nausea, diarrhea, cognitive dulling, sedation, fatigue, ataxia, and dizziness. The most severe adverse effects are hepatic failure, thrombocytopenia, pancreatitis, and potential for severe dermatological reactions. Divalproex carries a black box warning by the FDA regarding hepatotoxicity, teratogenicity, and pancreatitis (FDA, 2009a). Divalproex has not been approved by the FDA for treatment of PBD, yet it is used widely based on its effectiveness and efficacy in adults.

When starting divalproex in younger women, the risk of polycystic ovary syndrome should be discussed. The association was first suggested in 1993 in women who were using valproate as an antiepileptic drug, and it was seen as more significant during adolescence (Isojarvi et al., 1993). Since then, this association has been observed in several studies; a study of women with bipolar disorder found this association between valproate and polycystic ovarian disorder in 10% of the subjects, particularly in the younger group (aged thirteen to twenty-five years) (Joffe et al., 2006). This presentation has also been observed in women with epilepsy treated with valproic acid, more frequently within the same age range (Morrell et al., 2008; Talib & Alderman, 2013).

In 2009, Wagner and colleagues conducted an RCT to evaluate the efficacy of monotherapy with extended-release divalproex (maximum dose 35 mg/kg per day; serum levels 80 to 125 μg/mL). In this study, 150 subjects (aged 10 to 17 years) with BD I, manic or mixed episode, were randomized to receive

extended-release divalproex or placebo for 28 days. The results of this RCT were negative; there was no statistical difference between the two groups on the primary outcome as measured by change in mean YMRS score (−8.8 divalproex vs. −7.9 placebo; $p = 0.604$) or on secondary measures. The incidence of adverse effects was similar for both groups, except for weight gain, which was higher in the extended-release divalproex group. The most common adverse events were headache and vomiting (Wagner et al., 2009).

In one of the first reports of divalproex monotherapy for PBD, Pavuluri and colleagues (2005) conducted a six-month open trial to target acute symptoms in 34 subjects (aged 5 to 18 years) diagnosed with BD I, mixed episode, and a baseline YMRS score of more than 20. The primary outcome measures were YMRS and CDRS-R scores. Secondary measures were the Clinical Global Impression Scale for Bipolar Disorder (CGI-BP) and the CGAS. The response rate, as measured by at least a 50% change from baseline YMRS scores and a score of 40 or less on the CDRS-R, was 73.5% and the remission rate was 52.9%. Adverse events ranged from mild to moderate in terms of severity, with the most common being sedation, increased appetite, weight gain, and cognitive dulling (Pavuluri et al., 2005).

Kowatch and colleagues (2007) (unpublished data; presented at 2007 American Academy of Child and Adolescent Psychiatry meeting) enrolled 153 participants (aged 7 to 17 years) with BD I, manic or mixed episode, in an 8-week RCT comparing treatment with lithium, divalproex, or placebo. Response was defined as a Clinical Global Impressions–Improvement (CGI-I) score of 1 ("very much improved)," 2 ("much improved"), or 3 ("minimally improved)" compared to baseline. Results indicated that the response rates were 54% for divalproex, 42% for lithium, and 29% for placebo, with divalproex separating significantly from placebo. Lithium showed a trend toward efficacy but did not separate from placebo. The effect sizes for lithium and divalproex in this study were moderate. The findings from these divalproex trials are mixed, and at this time there is limited information on the effectiveness of monotherapy with divalproex in managing acute manic symptoms in children and adolescents.

Carbamazepine

The suggested starting dose of carbamazepine is 100 mg twice daily in patients aged 6 to 12 years of age and 100 mg three times daily in patients aged 12 years and older. Carbamazepine serum levels between 8 and 11 μg/mL are necessary for seizure control, but the level for therapeutic effect in PBD is unknown. The maximum dose is 1,000 mg/day in children aged 6 to 12 years and 1,200 mg/day in adolescents 13 years and older (Kowatch et al., 2011). The main side effects of carbamazepine include dizziness, drowsiness, vision changes, double vision, gastrointestinal disturbances, loss of appetite, dry mouth, weight gain, and potential for severe dermatological reactions. It is suggested that Asian patients be genetically screened for the human leukocyte antigen allele HLA-B*1502. Carbamazepine is generally not used with patients who test positive for this allelic version of the antigen, which is most common among Asian populations, since it is associated with a higher risk for developing toxic epidermal necrolysis or Stevens-Johnson syndrome. There is a black box warning concerning aplastic anemia and agranulocytosis, which occur rarely (FDA, n.d.).

The empirical evidence for the efficacy and tolerability of carbamazepine in treating PBD is limited. In 2010, Joshi and colleagues conducted a prospective 8-week open-label treatment trial of extended-release carbamazepine monotherapy in 27 children (aged s 6 to 12 years) diagnosed with BD I, BD II, or BD not otherwise specified with significant severity of manic, hypomanic, or mixed symptoms. The mean dose at study endpoint was 788 ± 252 mg/day. A total of 16 children (59%) completed the study. An intent-to-treat analysis showed statistically significant, although modest, improvement in symptoms of mania as measured by change in mean YMRS scores from baseline (−10.1 ± 10.2, $p < 0.001$). The mean YMRS score at study endpoint (21.8 ± 12.2) suggests that mania symptoms did not completely resolve. Additional analyses revealed significant improvements in depression and psychotic symptoms as measured by reduction in baseline CDRS-R and Brief Psychiatric Rating Scale (BPRS) scores respectively. Due to methodological limitations, including lack of a comparison group and small sample size, this study does not provide sufficient evidence for use of extended-release carbamazepine to treat PBD. To date, no RCTs have been conducted to assess the short- or long-term efficacy of using carbamazepine as a pharmacological intervention for PBD.

Oxcarbazepine

Oxcarbazepine is an analogue of carbamazepine with fewer side effects and better pharmacokinetic properties. It can be started at a dose of 8 to 10 mg/kg per day, dosed twice a day. The dose should be increased by 5 mg/kg per day every third day to the recommended maximum based on the child's weight. It does not require blood monitoring and there is less concern about hepatic enzyme induction associated with its use compared to carbamazepine (Goldstein et al., 2012; Kowatch et al., 2011).

Wagner and colleagues (2006) conducted a double-blind RCT where they enrolled 116 subjects (aged s 7 to 18 years) diagnosed with BD I, manic or mixed episode. Participants were randomized to receive either oxcarbazepine with flexible dosing (maximum dose 900 to 2,400 mg/day; mean dose 1,515 mg/day) or placebo for seven weeks. Mean YMRS scores decreased for patients in both groups; however, response rate (defined by at least a 50% reduction in baseline YMRS scores) did not statistically differ between the oxcarbazepine monotherapy (42%) and placebo (26%) groups. The most commonly reported adverse events included dizziness, nausea, somnolence, diplopia, fatigue, and rash, with the incidence of adverse events being higher in the oxcarbazepine group (90%) than in the placebo group (79%).

Lamotrigine

The starting dose for lamotrigine for an adolescent is 25 mg/day for two weeks with gradual increases to 200 to 400 mg/day. If the patient is on divalproex, then the starting dose of lamotrigine is 25 mg every other day for two weeks. For patients younger than 12 years, the dosing of lamotrigine is based on weight and follows guidelines depending on whether the patient is on an enzyme-inducing antiepileptic drug (Kowatch et al., 2011; Micromedex, 2014). Lamotrigine can cause some abdominal symptoms, dizziness, ataxia, headache, tremor, blurred vision, and diplopia and has the potential for severe dermatological reactions. There is a black box warning for Stevens-Johnson syndrome and toxic epidermal necrolysis (FDA, 2013).

There are no RCTs to date that have established the efficacy of lamotrigine to treat PBD. Biederman and colleagues (2010) conducted a prospective open 12-week trial of lamotrigine monotherapy in 39 participants (aged 6 to 17 years) with BD I, BD II, or BD not otherwise specified with manic, hypomanic, or mixed symptoms. The average dose was 160.7 ± 128.3 mg/day for participants under 12 years of age (N = 22) and 219.1 ± 172.2 mg/day in participants aged 12 to 17 years (N = 17). Clinical response was measured as having at least a 30% reduction in baseline YMRS scores or a CGI-I score of 2 or less (i.e., "much improved" or "very much improved"). The results of this trial showed a significant reduction of symptoms, with a response rate of 66% in participants under 12 years of age and 54% in participants greater than 12 years. Lamotrigine was also associated with improvement in depressive, ADHD, and psychotic symptoms. Twenty-five percent of participants discontinued due to adverse side effects. The most common adverse effects in the study were gastrointestinal issues, headaches, cold symptoms, and dermatological complaints. Among participants who discontinued due to an adverse effect, developing a skin rash was the most common reason for dropout. However, none of the skin rashes were life threatening or required hospitalization.

Topiramate

Topiramate is an anticonvulsant, indicated as monotherapy in patients 10 years of age and older with partial-onset or primary generalized tonic-clonic seizures and in adults for the prophylaxis of migraine headache. Topiramate can be started at 25 mg once daily and increased to 100 to 200 mg/day over 3 to 4 weeks. A lower starting dose and a slower rate of increase may decrease some of the negative cognitive effects of this drug (Kowatch et al., 2011).

Data from some open-label studies in adults suggest that topimarate might reduce symptoms of BD (Calabrese et al., 2001; Grunze et al., 2001); however, these findings have not been replicated through RCTs (Powers et al. 2004). Topimarate has been well tolerated in children and adolescents with epilepsy (Levinsohn, 2000), and DelBello and colleagues (2005) started conducting a pilot RCT to test its efficacy and safety as a monotherapy in the treatment of BD I in 56 patients (aged 6 to 17 years). Participants were randomized to receive either topimarate or placebo over a 4-week period. The trial was initially designed to enroll 230 subjects but was discontinued prematurely when a trial in adults with BD failed to demonstrate topimarate's efficacy over placebo

(DelBello et al., 2005; Powers et al., 2004). There was a reduction in mean YMRS scores from baseline in both groups; however, the difference in reduction was not statistically significant between groups. The decrease in sample size due to early termination likely left the study underpowered to be able to detect between-group differences, and therefore the results of this study are inconclusive. The most commonly reported adverse events included nausea, diarrhea, decreased appetite, paresthesia, and somnolence.

Second-Generation Antipsychotics

The SGAs (atypical antipsychotics) combine dopaminergic and serotoninergic properties to provide mood stabilization and treatment of acute symptoms of mania, including psychosis. The following SGAs have received FDA approval for the treatment of PBD (aged 10 to 17 years): aripiprazole (Abilify), quetiapine (Seroquel), risperidone (Risperdal), and olanzapine (Zyprexa; aged 13 to 17 years only) (Correll, 2011). Since 1995, there have been a total of 26 studies evaluating the efficacy of antipsychotic monotherapy for treatment of PBD using various study designs.

Risperidone

The treatment dose range for risperidone is 1 to 6 mg/day, with the most common side effects being fatigue, extrapyramidal side effects (EPS), elevated prolactin levels, weight gain, and elevations in cholesterol levels (Correll, 2011). Risperidone is the first atypical antipsychotic approved by the FDA for the acute treatment of BD I, manic or mixed episode, for children and adolescents aged 10 to 17 years (Correll, 2011).

One of the first RCTs to establish risperidone's efficacy in treating PBD was conducted by Haas and colleagues (2009), who randomized 169 participants (aged s 10 to 17 years) with BD I, manic or mixed episode, for 3 weeks to receive risperidone 0.5 to 2.5 mg/day ($N = 50$), risperidone 3 to 6 mg/day ($N = 61$), or placebo ($N = 58$). The purpose of having two dosing groups was to assess whether higher dose ranges were more effective and/or equally safe and tolerable as compared to lower dose ranges. The primary outcome measure in this study was change in YMRS scores from baseline. The results of this study indicated a statistically significant improvement in YMRS scores in both of the risperidone groups compared to placebo ($p < 0.001$). The clinical response rate (defined as a greater than 50% reduction from baseline in total YMRS scores) was observed to be 59% in the 0.5- to 2.5-mg risperidone group ($p < 0.002$) and 63% in the 3- to 6-mg risperidone group ($p < 0.001$) compared to 26% in the placebo group. Somnolence, headache, and fatigue were the most commonly reported adverse events. Comparison across different measures (YMRS, clinical response, CGI, and BPRS) between the two risperidone groups indicated that risperidone in the higher dosage range is no more efficacious than when administered in the lower dose range to treat PBD in this population. While both risperidone dose ranges were effective, the low-dose group was associated with a lower rate of discontinuation due to adverse events and a lower incidence of EPS-related adverse events. Overall, the lower dose range had a more favorable safety profile, and this was similar to safety data from other risperidone studies to treat BD in adults and children (Haas et al., 2009).

In the first double-blind study of its kind, Pavuluri and colleagues (2010) randomized 66 participants with PBD (aged 8 to 18 years) to receive treatment with divalproex (60 to 120 μg/mL, $N = 33$) versus risperidone (0.5 to 2 mg/day, $N = 33$) over a six-week period. A mixed-effects regression model of YMRS scores by active drug and time found that patients in the risperidone group improved more rapidly than those in the divalproex group. Patients receiving risperidone also had a higher response rate based on more than 50% change in baseline YMRS scores (78.1% for risperidone vs. 45.5% for divalproex, $p < 0.01$), a higher response rate based on more than 50% improvement in CDRS-R scores (65.5% for risperidone vs. 42.4% for divalproex, $p < 0.01$), and higher remissions rates based on a YMRS score of 12 or less and a CDRS-R score of 28 or less (62.5% with risperidone vs. 33.3% with divalproex, $p < 0.05$). Response rates for risperidone were similar to those found in other studies (Biederman et al., 2005). There were no significant differences between groups on safety. However, there was a lower dropout rate in the risperidone group (24%) compared to the divalproex group (48%), the most common reason for dropout in the divalproex group being increased irritability. There was no significant weight gain in this study; however, these results should be interpreted with caution due to the study's small sample size and the frequent documentation of weight gain as a side effect in other risperidone trials. This was the first randomized trial

to establish preliminary evidence that risperidone had a more rapid effect and higher reduction of mania symptoms compared to divalproex in the acute treatment of PBD (Pavuluri et al., 2010).

The results of Pavuluri and colleagues' study (2010) were further extended by another head-to-head RCT conducted by Geller and colleagues (2012) that compared the effect of risperidone, lithium, and divalproex sodium in the acute treatment of BD I, manic or mixed episode. In this study, 279 participants (aged 6 to 15 years) were randomly assigned to receive risperidone (maximum dose 4 to 6 mg), lithium (maximum dose 1.1 to 1.3 mEq/L), or divalproex sodium (maximum dose 111 to 125 μg/mL) for eight weeks. The primary outcome measure was the Clinical Global Impressions for Bipolar Illness Improvement-Mania (CGI-BP-IM) and treatment response was defined as a rating of 1 ("very much improved") or 2 ("much improved") compared to baseline. Patients in the risperidone group had a higher response rate (68.5%) compared to those receiving lithium (35.6%, $p < 0.001$) or divalproex (24%, $p < 0.001$). There were no significant differences in response rates between the lithium and divalproex groups. Consistent with previous studies, the risperidone group had a lower discontinuation rate than the lithium group. Although more efficacious in the acute management of PBD, risperidone was associated with significantly higher weight gain, increase in body mass index (BMI), and increase in prolactin levels compared to treatment with lithium or divalproex.

Quetiapine

The treatment dose range for quetiapine is 150 to 750 mg/day, with the main adverse side effects being sedation, dizziness, gastrointestinal upset, weight gain, dyslipidemia, and dysglycemia (Correll, 2011).

The efficacy and safety of quetiapine monotherapy was investigated by Pathak and colleagues (2013) in a multisite RCT with 284 participants (aged 10 to 17 years) diagnosed with BD I with manic episodes. Participants were randomized to receive quetiapine 400 mg/day ($N = 95$), quetiapine 600 mg/day ($N = 98$), or placebo ($N = 91$) over a period of three weeks. Quetiapine at both doses was associated with significantly greater improvement in total YMRS scores (primary outcome measure) compared to placebo ($p < 0.001$). Participants in both quetiapine treatment arms had significantly greater response rates (64% for quetiapine 400 mg/day, 58% for quetiapine 600 mg/day, 37% for placebo) and remission rates (45% for quetiapine 400 mg/day, 52% for quetiapine 600 mg/day, 23% for placebo). Results indicated statistically significant improvements in both quetiapine groups on other outcome measures, including the CGAS, CGI-BP Severity of Illness, and CGI-BP-Global Improvement scores, compared to placebo. Like risperidone, quetiapine was also associated with a more rapid onset of effect, separating from placebo by as early as day 4. The adverse events reported in this study were broadly consistent with those reported in adult studies of BD and were most commonly somnolence, sedation, dizziness, and headache. The researchers noted that 45% of the sample had comorbid ADHD and 15% of these individuals were also on stimulants; however there were no significant differences in adverse events reported by patients taking other psychotropic medication compared to those taking quetiapine alone (Pathak et al., 2013).

In another head-to-head double-blind RCT, DelBello and colleagues (2006) compared the efficacy and safety of quetiapine versus divalproex among 50 adolescents (aged 12 to 18 years) with BD I, manic or mixed episode. Participants were randomized to 28 days of treatment with either quetiapine (400 to 600 mg/day) or divalproex (serum level 80 to 120 μg/mL). While quetiapine led to more rapid improvement in manic symptoms than divalproex, and both were associated with significant improvement in YMRS scores from baseline, the difference between the groups in YMRS change from baseline was not statistically significant. Secondary outcome measures such as response rate and remission were higher for participants on quetiapine compared to divalproex. The treatment groups did not differ in terms of incidence or severity of adverse events, and rates of completion were the same in both groups. The findings of this study suggest that quetiapine is at least as effective and well tolerated as divalproex in the treatment of acute PBD.

Aripiprazole

The treatment dose range for aripiprazole is 10 to 30 mg, with the main side effects being sedation, stomach discomfort, and EPS (Correll, 2011). There have been two recent positive RCTs that have established the efficacy of aripiprazole as monotherapy for the treatment of PBD.

Findling and colleagues (2009) randomized 296 participants (aged 10 to 17 years) diagnosed with BD I, manic or mixed episode, to receive aripiprazole 10 mg/day, aripiprazole 30 mg/day, or placebo over an acute 4-week treatment period. The study found significantly greater reductions in symptoms of mania in both aripiprazole treatment groups compared to placebo as measured by change from baseline in total YMRS scores. Both aripiprazole dose groups were also superior to placebo on key secondary measures. Remission was defined as YMRS total score of 12 or less and a CGI-BP severity score of 2 or less; significantly higher remission rates were observed in the aripiprazole 10 mg/day (25%) and aripiprazole 30 mg/day (48%) treatment arms compared to placebo (5%). Clinical response (at least 50% reduction from baseline YMRS total score) was observed in 44.8%, 63.6%, and 26.1% of participants in the aripiprazole 10 mg, 30 mg, and placebo groups respectively ($p < 0.01$ for both doses vs. placebo). Aripiprazole did not significantly reduce depressive symptoms in these groups. The most commonly reported adverse events were somnolence and EPS, occurring more frequently in the aripiprazole 30 mg group than the aripiprazole 10 mg group. There was at least one serious adverse event in each treatment group (aripiprazole 10 mg, $N = 5$; aripiprazole 30 mg; $N = 2$; placebo, $N = 5$). In the aripiprazole 10 mg group, the serious adverse events were accidental overdose, grand mal seizure, respiratory arrest, aggression, oppositional behavior, and suicidal ideation. In the aripiprazole 30 mg and placebo groups, all serious adverse events were "exacerbation of bipolar disorder."

In another double-blind placebo-controlled trial conducted by Tramontina and colleagues (2009), 43 participants (aged 8 to 17 years) with comorbid PBD, manic or mixed episode, and ADHD were randomized to receive aripiprazole monotherapy (maximum dose 20 mg/day; $N = 18$) or placebo ($N = 20$) for a 6-week period. The aripiprazole group proved superior to placebo on multiple primary and secondary outcome measures, including reduction in YMRS scores from baseline ($p < 0.02$), Children Mania Rating Scale-Parent Version (CMRS-P) ($p = 0.02$), and CGI-Severity ($p = 0.04$). Findings indicated significantly higher response rates (88.9% vs. 52%, $p = 0.02$) and remission rates (72% vs. 32%, $p = 0.01$) in the aripiprazole group when compared to placebo. There were no significant differences on ADHD or depressive symptoms between groups. Some of the commonly reported adverse events included somnolence, tiredness, increased appetite, headache, and nausea.

Several open-label trials have also supported the efficacy and tolerability of aripiprazole in the treatment of PBD and have been summarized in Table 9.1 (Findling et al., 2008b, 2011; Gibson et al., 2007; Tramontina et al., 2007).

Olanzapine

Olanzapine carries an FDA approval for youths aged 13 to 17 with BD I for mood stabilization and treatment of acute symptoms of mania, including psychosis. The treatment dose range in pediatrics is 5 to 20 mg daily; olanzapine can cause increased appetite, somnolence, sedation, weight gain, dyslipidemia, and dysglycemia (Correll, 2011).

Tohen and colleague (2007) conducted one of the largest double-blind placebo-controlled trials; it enrolled 161 participants (aged 13 to 17 years) with BD I, manic or mixed episode. Participants were randomized to receive olanzapine at a flexible dose (2.5 to 20 mg/day; $N = 107$) or placebo ($N = 54$) for three weeks. Olanzapine was superior to placebo, as indicated by significantly greater reduction in YMRS total scores from baseline among participants in the olanzapine group (–17.65 vs. –9.99, $p \leq 0.001$). Participants receiving olanzapine treatment had significantly higher response and remission rates compared to participants in the placebo arm (response: 48.6% vs. 22.2%, $p = 0.002$; remission: 35.2% vs. 11.1%, $p = 0.001$). Weight gain and increase in BMI were significantly greater in the olanzapine group compared to the placebo group (weight gain: 3.7 kg vs. 0.3 kg, $p < 0.001$; BMI: 1.18 vs. 0.02; $p < 0.001$), as was the frequency of other side effects such as drowsiness and sedation. Furthermore, in the olanzapine group, significant increases were observed in systolic blood pressure ($p = 0.001$), fasting blood glucose ($p = 0.002$), total cholesterol ($p = 0.001$), and prolactin levels ($p < 0.001$). Improved functioning according to the CGAS scores was also observed. This trial established the efficacy of olanzapine as monotherapy during acute treatment of PBD but also highlighted multiple metabolic side effects of significant concern (Tohen et al., 2007).

Ziprasidone

The treatment dose range for ziprasidone is 80 to 160 mg, with the following adverse side effects: sedation,

headaches, and gastrointestinal disturbances. There appears to be less weight gain among patients taking ziprasidone when compared to risperidone and olanzapine. Ziprasidone is contraindicated in patients with a known history of QTc prolongation or arrhythmia (Correll, 2011).

There are limited published data on the efficacy and safety of ziprasidone for the treatment of PBD. In an eight-week, open-label trial, 21 youth (aged 6 to 17 years) with BD I, manic or mixed episode, or *DSM-IV*-defined BD not otherwise specified received ziprasidone monotherapy. Ziprasidone was associated with significant improvement in mean YMRS scores, with a response rate of 57% (CGI-I ≤ 2) (Biederman et al., 2007). DelBello and colleagues (2008) assessed ziprasidone's tolerability in an open-label trial with 63 youth (aged 10 to 17 years) receiving ziprasidone (80 or 160 mg/day in two divided doses) over a three-week fixed-dose period. They concluded that adverse events were more common in the high-dose group than the low-dose group.

In a four-week, double-blind, placebo-controlled trial, 238 participants (aged 10 to 17 years) were randomized to receive ziprasidone or placebo. Target ziprasidone doses ranged from 80 to 160 mg/day for participants weighing more than 45 kg and from 40 to 80 mg/day for participants weighing less than 45 kg. The findings from this RCT have not been published but were presented at the APA's 161st annual meeting and are available on the FDA website (DelBello et al., 2008). The primary efficacy measure was the change in YMRS total scores from baseline. Ziprasidone had a higher response rate for the treatment of mania compared to placebo (62% vs. 35%; $p < 0.001$). Patients receiving ziprasidone 40 to 80 mg/day showed less improvement than the group receiving 80 to 160 mg/day, but it was unclear whether this difference was due to the dose or a weight effect, since the dosing mechanism is related to patient weight. The most frequent side effects reported were dystonia, headache, and sedation. Ziprasidone, however, has not received FDA approval for treatment of PBD due to quality-control issues that occurred with this particular study (FDA, 2009b).

Clozapine

The pediatric treatment dose for clozapine ranges from 50 to 600 mg/day. Common adverse events are sedation, weight gain, increased salivation, seizures, myocarditis, and potentially lethal agranulocytosis (which limits the use of this medication to patients who have not responded to other treatment interventions) (Correll, 2011).

There are currently no RCTs that have established the efficacy and safety of clozapine to treat PBD. Masi and colleagues (2002) conducted a small open trial of clozapine in 10 inpatient adolescents (aged 12 to 17 years) with severe BD I, manic or mixed episode, who had not improved after treatment with SGAs or mood stabilizers. Significant improvement was observed on multiple outcome measures, including CGI-S, CGI-I, YMRS, BPRS, and CGAS, at hospital discharge, which was 15 to 28 days after clozapine treatment had been initiated. Data from open trials such as this one suggest that clozapine may be beneficial as an intervention for treatment-resistant PBD.

Combination Treatment Trials

When youth with PBD do not respond to monotherapy with one of the agents described previously, combination medication treatment is often initiated to help reduce manic or mixed symptoms (Bhangoo et al., 2003). Data from recent combination treatment studies are reviewed below. The majority of these studies are open-label trials with small sample sizes and treatment offered across varying time periods; therefore, results from these studies should be interpreted with caution.

Combined Treatments of Mood Stabilizers and Atypical Antipsychotics

In 2002, DelBello and colleagues investigated the efficacy and tolerability of quetiapine as an adjunctive treatment to divalproex among 30 participants (aged 12 to 18 years) with BD I, manic or mixed episode. All participants received divalproex 20 mg/kg on day 0 and were then randomized to adjunctive treatment with quetiapine (titrated to a maximum dose of 450 mg/day) or placebo for six weeks. Both groups had reduced YMRS scores at the end of the study; however, the divalproex-plus-quetiapine group had significantly greater reduction in YMRS scores from baseline to study endpoint compared to the divalproex-plus-placebo group ($p = 0.03$). Response rates were also significantly higher in the divalproex-plus-quetiapine group (87%) versus the divalproex-plus-placebo group (53%). The most common adverse side effects in both groups

were sedation, headache, nausea, and gastrointestinal irritation, with sedation being significantly more common in the divalproex-plus-quetiapine group compared to the divalproex-plus-placebo one. Subjects in the divalproex-plus-quetiapine group gained more weight than those on divalproex alone (4.2 ± 3.2 kg and 2.5 ± 2.1 kg respectively); however, this difference was not statistically significant. These results indicated that quetiapine in combination with divalproex might be more efficacious in treating manic or mixed symptoms in PBD than divalproex alone.

Pavuluri and colleagues conducted two open-label trials that assessed the efficacy of risperidone in combination with a mood stabilizer for acute treatment of PBD. In the first trial in 2004, 37 subjects (aged 5 to 18 years) with BD I, manic or mixed episode, were sequentially assigned to receive risperidone (3 mg/day) adjunctive to either lithium (0.6 to 1.0 mEq/L) or divalproex (50 to 120 µg/mL) over a 6-month period. Participants in both groups showed significant improvements in YMRS, CGI-S, and CGI-I scores from baseline; however, differences between groups were not statistically significant. The response rate (based on at least 50% change in baseline YMRS scores) was comparable in both groups (82.4% for risperidone plus lithium and 80% for risperidone plus divalproex). There were no significant differences in adverse side effects between groups. In 2006, Pavuluri and colleagues further explored the combination treatment of risperidone and lithium among 38 subjects (aged 4 to 17 years) with preschool-onset BD. All participants first received lithium monotherapy (single dose of 150 or 300 mg/day) for eight weeks. Of the 38 participants, 21 failed to have an adequate response or relapsed after an initial response and were augmented with risperidone (maximum dose 2 mg/day) for up to 11 months. The response rate for the combined medication group (as defined by at least 50% change in baseline YMRS scores) was 85.7%, and 57.1% maintained remission at the end of the 12-month period.

Wozniak and colleagues (2009) conducted two partially concurrent 8-week open-label trials to test the efficacy and safety of olanzapine alone and olanzapine augmented with topimarate in 40 participants (aged 6 to 17 years) diagnosed with BD I or BD II. Participants received either olanzapine monotherapy (N = 17; mean dose 8.6 ± 3.4 mg/day) or the combination of olanzapine (mean dose 9.9 ± 5.2 mg/day) plus topimarate (70.5 ± 30.5 mg/day) (N = 23). Both groups demonstrated statistically significant improvement at study endpoint as measured by change in YMRS and CGI-I scores, but differences between groups were not significant. There was a statistically significant increase in weight from baseline in both groups; however, the olanzapine-only group experienced twice as much weight gain than the olanzapine-plus-topimarate group (5.3 kg vs. 2.5 kg, p = 0.006).

Combined Treatments of Two Mood Stabilizers

Findling and colleagues (2003) examined the combination of lithium (30 mg/kg per day) and divalproex (20 mg/kg per day) in an open-label trial with 90 participants (aged 5 to 17 years) with BD I or BD II, manic or hypomanic episodes for up to 20 weeks. There was significant reduction in manic symptoms, depressive symptoms, and overall functioning at week 8 and at the end of the study as measured by changes in YMRS, CDRS-R, and CGAS scores from baseline. The mean length of treatment in the study was 11.3 weeks. Forty-seven percent of participants met criteria for clinical remission as defined by CDRS-R 40 or less, YMRS 12.5 or less, and CGAS 51 or more for four consecutive weeks.

Findling and colleagues (2006) examined the same combination treatment in another 8-week open-label trial to assess its efficacy in restabilization among 38 patients (aged 5 to 17 years) who had relapsed after monotherapy with either lithium or divalproex. Similar to the previous trial, significant improvements were observed in manic symptoms, depressive symptoms, and overall functioning as measured by changes in YMRS, CDRS-R, and CGAS scores from baseline. At the end of the eight weeks of combination treatment, 89.5% (n = 34) of the participants were successfully restabilized, but four participants required adjunctive antipsychotic treatment to address residual symptoms. While findings of these two open-label trials suggest that the combination of lithium and divalproex may be efficacious in treating mania symptoms in the short term, due to the lack of a comparison monotherapy treatment arm, it cannot yet be concluded that combination treatment is superior to monotherapy with lithium or divalproex.

ACUTE TREATMENT OF BIPOLAR DEPRESSION

Depressive episodes are the most common manifestation of bipolar disorder in youth. In PBD, depressive episodes are characterized by sad mood and irritability along with hopelessness and anhedonia and are associated with increased suicidality (Wozniak et al., 2004). Compared to adults, depressive episodes in PBD are more frequent and longer in duration (Geller et al., 2004) and are commonly undiagnosed in children with BD (Chang, 2009). There is a general lack of controlled studies of pharmacotherapy for bipolar depression in children. This is partially due to the significant concern of suicide risk and exacerbation or induction of mania when using antidepressants to treat bipolar depression (Olfson et al., 2006).

Lithium

Patel and colleagues (2006) conducted an open-label trial where 27 inpatient adolescents (aged 12 to 18) were treated with lithium (30 mg/kg per day, titrated to 1.0 to 1.2 mEq/L) for six weeks. There were significant reductions in the CDRS-R score, which was the primary outcome measure, from baseline to study endpoint. The response rate was 48% (at least 50% reduction in CDRS-S from baseline), and 30% of the participants achieved remission (CDRS-R score 28 or less and CGI-BP 2 or less). The most common adverse side effects in this sample were headaches (74%), nausea or vomiting (67%), stomachache (30%), and abdominal cramps (19%).

Lamotrigine

Chang and colleagues (2006) conducted a small open-label trial of lamotrigine (12 to 25 mg/day) to treat 20 adolescents (aged 12 to 17 years) who were diagnosed with BD I, BD II, or BD not otherwise specified and who were experiencing a depressive episode. Lamotrigine was administered as monotherapy or adjunct to other psychotropic medications such as stimulants, lithium, or antipsychotics. At the end of the study, 84% of participants responded to primary criteria (CGI-I 2 or less), 63% responded to secondary criteria (at least 50% decrease in CDRS-R scores), and 58% attained remission (CDRS-R 28 or less and CGI-S 2 or less). Seven of the 20 participants received lamotrigine as adjunctive medication; however, there were no differences in CDRS-R scores compared to those on lamotrigine monotherapy. There were no serious adverse events in this study, and the adverse side effects reported included headache, fatigue, sweating, nausea, and trouble sleeping. While this study suggests some potential benefit of lamotrigine in the treatment of bipolar depression, it had several methodological limitations, such as the lack of a placebo arm or use of concomitant medications. Controlled trials with larger samples would be needed to establish the efficacy of this drug for use in this patient population.

Quetiapine

The only RCT for bipolar depression in youth was conducted by DelBello and colleagues in 2009. In this RCT, 32 participants (aged 12 to 18 years) with a depressive episode associated with BD I were randomized to treatment with quetiapine (300 to 600 mg/day) versus placebo for eight weeks. There was no statistically significant difference between the two groups on the primary outcome measure (change in CDRS-R scores from baseline), response rate (at least 50% decrease in CDRS-R scores from baseline), or remission rate (CDRS-R 28 or less and CGI-BP-I 2 or less). This study had a very high placebo response rate (67%), which according to the authors could be due to limitations of rating scales and outcome measures used in this study. Findings of this study suggest that quetiapine may not be superior to placebo in improving depressive symptoms among youth with BD and additional research in this area is needed.

Antidepressants

There are limited data on antidepressant treatment for depression within the context of PBD. Biederman and colleagues (2000) did a chart review of 59 patients with PBD and found that when treated with antidepressants, children with bipolar depression improved but they were three times more likely to experience a subsequent manic episode. The use of mood stabilizers was helpful in improving manic symptoms but did not change the course of depression, while selective serotonin reuptake inhibitors (SSRIs) did not improve manic symptoms. In the *Treatment Guidelines for Children and Adolescents with Bipolar*

Disorder, Kowatch and colleagues (2005) discouraged antidepressant monotherapy trials and suggested that SSRIs or bupropion should be considered after mood stabilization.

MAINTENANCE TREATMENT OF PEDIATRIC BIPOLAR DISORDER

PBD is an illness that has a chronic and relapsing course, which often requires long-term treatment (Birmaher et al., 2009). There are very limited data to guide clinical recommendations on maintenance treatment of PBD, with current evidence from three RCTs and a few open-label studies. The medications that have been assessed in these trials for efficacy in maintenance of symptom remission are lithium, divalproex, lamotrigine, and aripiprazole.

Mood Stabilizers

Kafantaris and colleagues (2004) conducted the first placebo-controlled discontinuation trial of lithium among 40 youth (aged 12 to 18 years) with BD I, manic episode who had previously responded to open-label treatment with lithium for up to 4 weeks (Kafantaris et al. 2003). These participants were then randomly assigned to either continue lithium or discontinue and switch to placebo for two weeks. At the end of the 2-week period, both lithium and placebo groups had similar rates of symptom exacerbation as measured by CGI-I scores: 52.6% for lithium and 61.9% for placebo. Despite promising results in the open-label acute treatment phase, lithium was not found to be superior to placebo in sustaining response and remission of symptoms. Researchers suggested that a longer period of treatment with lithium might be required to establish its efficacy for maintenance treatment of PBD.

Findling and colleagues (2005) followed 139 participants (aged 5 to 17 years) with BD I or BD II who had previously been stabilized on combination therapy of lithium and divalproex. Of these 139 participants, 60 met remission criteria for four consecutive weeks and were then randomly assigned to discontinue one of the agents for 76 weeks. The primary outcome measure was time to premature discontinuation for treatment of emerging symptoms of relapse. There was no difference in time to recurrence of symptoms between the lithium (114 ± 57.4 days) and divalproex (112 ± 56 days) monotherapy groups. Divalproex was not found to be superior to lithium monotherapy in the maintenance treatment for youth with PBD who had achieved remission with the combination treatment of lithium and divalproex (Findling et al., 2005).

In 2009, Redden and colleagues examined 226 participants (aged 9 to 17 years) over six months of continuation treatment following acute treatment with extended-release divalproex sodium for BD I, manic or mixed episodes. It was prescribed at 15 mg/kg per day, with a maximum dosage of 35 mg/kg per day. Of the 225 participants enrolled, 109 (44.4%) took divalproex for at least 180 days. The three most common side effects were weight gain (16%), nausea (9%), and increased appetite (8%), and the overall safety profile was comparable to that found in other PBD studies of divalproex. There was a 12.4-point decrease in mean YMRS scores from baseline; however, due to the lack of a placebo-controlled arm, interpretations from these findings are limited.

In another open-label study, Pavuluri and colleagues (2009) examined the effects of maintenance treatment with lamotrigine in 46 patients (aged 8 to 18 years) with BD I, mixed or manic episode or BD II, hypomanic episode. During the first 8-week period, lamotrigine was slowly increased to a therapeutic dose (150 mg in patients weighing 30 kg or less, or 200 mg in those weighing more than 30 kg) in combination with SGAs to stabilize acute symptoms. SGAs were withdrawn over the last two weeks of this acute treatment period, at the end of which patients were receiving lamotrigine alone. Then, remitted patients continued to receive maintenance treatment with lamotrigine monotherapy for a 6-week period. At the end of the 14 weeks, the mania response rate based on the YMRS was 71%, the depression response rate on the CDRS-R was 82%, and the remission rate was 56%. Researchers also found that depressive symptoms continued to decline further with lamotrigine monotherapy in the second 6-week maintenance phase. Of the subjects in remission at the end of the acute 8-week treatment, 23% relapsed by week 14. The most commonly reported adverse side effects included sedation (23.7%), stomachache (19.6%), increased urination (10.9%), and increased appetite (10.9%); three subjects dropped out of the study after developing a benign rash. The findings of this study indicate that lamotrigine appears to be effective in maintaining the response of manic and depressive

symptoms in PBD after acute combination treatment with SGAs. Furthermore, results suggest that SGAs can potentially be withdrawn after reaching a therapeutic dose of lamotrigine without complete relapse of symptoms over a 6-week period.

Second-Generation Antipsychotics

Findling and colleagues (2012) studied the long-term efficacy of aripiprazole in a double-blind placebo-controlled trial with 60 patients (aged 4 to 9 years) diagnosed with BD I or BD not otherwise specified. These participants had previously been part of an acute open trial during which their symptoms were stabilized with aripiprazole for up to 16 weeks (Findling et al., 2011). If they met response criteria for four consecutive weeks, they were then randomly assigned to continued aripiprazole treatment (mean dose 6.4 ± 2.1 mg/day; $N = 30$) or placebo ($N = 30$) for up to 72 weeks. Patients in the aripiprazole group stayed in the study for a significantly longer time (mean weeks 25.93 ± 3.91) compared to those in the placebo group (mean weeks 3 ± 0.57; $p = 0.003$). The time to discontinuation from the study due to a mood event was also significantly longer in the aripiprazole group (mean weeks 25.93 ± 5.81) than in the placebo group (mean weeks 3.10 ± 0.53; $p = 0.005$), with the most common reason for discontinuation being lack of efficacy. There were no significant group differences on symptoms as rated by the YMRS, CDRS-R, CGAS, or CGI-S. Children in the aripiprazole group were more likely to report musculoskeletal and stomach pain and had significantly greater weight gain. The results of this study suggested that aripiprazole may be beneficial in the long-term treatment of children with BD. However, both groups showed a high rate of study dropout (70% for aripiprazole and 90% for placebo), indicating that even though aripiprazole was superior to placebo during maintenance, it was not sufficient to keep youth stable over longer periods of time.

TREATMENT OF COMORBID CONDITIONS

ADHD

ADHD is among the most common comorbidities in PBD, occurring in 30% to 40% of adolescents with PBD (Geller & Luby, 1997). It has been associated with decreased treatment response for acute mania (Consoli et al., 2007). Scheffer and colleagues (2005) conducted a two-stage trial with 42 participants (aged 6 to 17 years) with BD I or BD II. In the first phase, participants received open treatment with divalproex for eight weeks. Participants were eligible to enter the second phase if they had an improvement in manic symptoms based on the YMRS but no improvement in ADHD symptoms based on CGI-I scores ($N = 30$). The second phase consisted of a 4-week double-blind crossover trial of mixed amphetamine salts (MAS; 5 mg twice daily) and placebo (2 weeks in each condition). Participants continued receiving divalproex during the 4-week crossover trial. There were significant improvements in ADHD symptoms in the MAS group, but no differences on change in YMRS scores between groups. The adverse side effects reported included abdominal pain, diarrhea, nausea, and increased appetite, and were not significantly different between the open-label and crossover trials. MAS did not increase mania symptoms in either of the groups. These findings were replicated in a similar 4-week double-blind placebo-controlled crossover trial in 16 youth (aged 5 to 17 years) diagnosed with comorbid PBD and ADHD (Findling et al., 2007). Prior to randomization, patients were being treated with mood stabilizers (lithium, divalproex, or a combination of both). During this crossover study, patients were randomized to 1 week of placebo, 1 week of methylphenidate (MPH) 5 mg twice daily, 1 week of MPH 10 mg twice daily, and 1 week of MPH 15 mg twice daily. At the end of the study, each participant's "best dose week" was determined and compared to placebo on primary and secondary efficacy measures. There were significant differences in ADHD symptoms among patients treated with MPH at any dose versus placebo. There were no group differences for manic or depressive symptoms. This study was underpowered to be able to detect significant differences between the different dose levels of MPH.

Zeni and colleagues (2009) conducted a randomized crossover double-blind controlled trial with 16 youth (aged 8 to 17 years) diagnosed with BD I or BD II comorbid with ADHD. Manic symptoms in these youth had previously responded to treatment with aripiprazole, but they still had clinically significant ADHD symptoms. Participants were randomized to receive aripiprazole and MPH (0.3 mg/kg per day) or aripiprazole and placebo for two weeks each. One of the goals of the study was to determine whether mania symptoms would worsen when adding a stimulant to

antipsychotic treatment in these comorbid cases of PBD and ADHD. The results of this study indicated that there were no significant differences between the MPH and placebo groups on manic or ADHD symptoms as measured by change in YMRS and Swanson, Nolan, and Pelham Scale IV Version (SNAP-IV) scores respectively. There were no significant differences in depressive symptoms as measured by change in clinician-rated CDRS-S scores; however, significant improvement in depressive symptoms was observed based on a secondary self-report measure. There were no significant differences in side effects between the groups, and MPH was no more effective than placebo in improving PBD or ADHD symptoms.

In these three RCTs, manic symptoms were first stabilized with either a mood stabilizer (lithium or divalproex) or an SGA (aripiprazole). The findings were mixed on whether or not stimulants improved ADHD symptoms when added to one of these compounds. However, stimulants did not make manic symptoms worse in any of these trials. RCTs with more rigorous methodology and larger sample sizes are needed to establish the efficacy of stimulants in decreasing ADHD symptoms in youth with PBD. Until more data are obtained, the American Academy of Child and Adolescent Psychiatry treatment guidelines currently recommend that treatment in youth with comorbid PBD and ADHD should be sequential: Bipolar symptoms should be treated first to stabilize mood, and if ADHD symptoms persist, they can be treated with stimulants (Kowatch et al., 2005).

Anxiety

Anxiety disorders are also highly prevalent in youth with PBD, ranging from 37% to 60% depending on bipolar subtype (Axelson et al., 2006; Kowatch et al., 2005). They are associated with severe depressive symptoms, increased risk of mania or hypomania, and lower likelihood of recovery. Currently, no treatment studies have targeted comorbid anxiety in PBD. Treatment guidelines by Kowatch and colleagues (2005) recommend the use of psychosocial interventions that are known to be efficacious in treating anxiety, such as cognitive-behavioral therapy or interpersonal psychotherapy. If medication is needed, it is recommended to first stabilize mood symptoms, particularly mania, before initiating treatment with SSRIs.

Substance Abuse Disorders

The lifetime prevalence of substance abuse disorders in PBD ranges from 6.7% to 9.8% (Axelson et al., 2006). Treatment guidelines recommend that both conditions should be treated simultaneously without delay (Kowatch et al., 2005). This can generally be managed on an outpatient basis, but sometimes an inpatient stay at a hospital or rehabilitation center may be required. Geller and colleagues (1998) conducted the first RCT for lithium in adolescents with BD I, manic or mixed episode, with secondary substance dependence ($N = 25$). In addition to having significant improvements in mood symptoms, participants treated with lithium were less likely to have a positive drug urine test compared to subjects receiving placebo ($p = 0.028$).

SAFETY CONCERNS

Mood Stabilizers

Due to their narrow therapeutic window, lithium, divalproex, and carbamazepine need careful monitoring. The most severe adverse events associated with these medications are seizures, cardiac arrhythmias, coma, and, in extremely rare cases, death (in the case of lithium) (Findling & Pavuluri, 2008; Geller et al., 1998). In the case of divalproex, liver failure and pancreatitis are rare but present a serious concern. For carbamazepine, aplastic anemia, agranulocytosis, and hyponatremia are very serious rare complications. These three mood stabilizers are teratogenic and therefore affect the development of the fetus. It is key to monitor a patient's safety with laboratory assessments and electrocardiograms, and to do a pregnancy test prior to starting lithium, divalproex, or carbamazepine. Lamotrigine can cause a fatal necrotizing rash called Steven-Johnson syndrome and toxic epidermal necrolysis.

Second-Generation Antipsychotics

The most common side effects of SGAs are weight gain and metabolic abnormalities, including diabetes mellitus and hyperlipidemia. Olanzapine and clozapine are associated with the highest amount of weight gain in both adults and children. Other concerning adverse side effects include EPS, prolactin elevation

(primarily for risperidone), intracardiac conduction effects such as QTc prolongation (ziprasidone), and agranulocytosis and seizures (clozapine).

Safety Assessment

Youth should be carefully monitored when receiving pharmacological treatment for PBD with mood stabilizers and/or atypical antipsychotics. Personal and family medical history should be obtained at baseline as well as annually. At each visit, information on lifestyle behaviors, sedation, height, weight, BMI percentile, and BMI *z*-scores should be obtained. BMI can be calculated in kg as follows: weight (kg) / [height (m)]^2 or in pounds as follows: weight (lb) / [height (in)]^2 × 703. BMI *z*-scores, also called BMI standard deviation (s.d.) scores, are measures of relative weight adjusted for the child's age and sex. Given a child's age, sex, BMI, and an appropriate reference standard, a BMI *z*-score (or its equivalent BMI-for-age percentile) can be determined (Correll, 2008; Must & Anderson, 2006). At baseline, during titration, and for every three months thereafter, sexual or reproductive dysfunction should be assessed. Parkinsonism and akathisia should be assessed at these points as well as annually. At baseline, three months after baseline, and annually, tardive dyskinesia, liver function tests, blood pressure, and pulse should be reviewed. Fasting blood glucose and lipids should be obtained at baseline, three months after baseline, and every six months thereafter. Electrolytes, a full blood count, and renal and liver function should be assessed annually; blood count should be monitored more frequently if the patient is taking clozapine. If a patient is taking ziprasidone at the maximum dose, an electrocardiogram should be obtained. If male patients develop gynecomastia or galactorrhea, or female patients develop amenorrhea or oligomenorrhea, prolactin levels should be tested (Correll, 2008).

PSYCHOSOCIAL TREATMENTS FOR PEDIATRIC BIPOLAR DISORDER

The symptoms of PBD are associated with significant psychosocial impairment in multiple domains across a child's development (Weinstein et al., 2013). These include poor academic performance, neurocognitive deficits, poor social and coping skills, and high levels of interpersonal conflict (Geller et al., 2000, 2002; Goldstein et al., 2006; Henin et al., 2007; Kim et al., 2007; Pavuluri et al., 2006b; Rucklidge, 2006; Wilens et al., 2003). Due to the nature and extent of these psychosocial impairments in PBD, experts in the field concur that high-quality, evidence-based psychosocial interventions are needed to improve the course of treatment for this illness (McClellan et al., 2007). Although pharmacotherapy continues to be the first-line treatment for PBD, growing literature suggests that psychosocial interventions are also important to provide family members with a more comprehensive understanding of the illness and appropriate coping strategies. In addition, adverse side effects, poor response to medication, and the inability to address the social, academic, and family factors that affect treatment outcomes through pharmacotherapy also highlight the need for adjunctive psychosocial treatments (McClellan et al., 2007).

This section reviews the evidence base for psychosocial interventions in the treatment of PBD. These interventions are primarily designed to be used as adjunctive treatments with pharmacotherapy and/or TAU. While research has made significant advances in the past decade, data from type 1 studies are limited. This section summarizes data for six types of psychotherapies to treat PBD and includes studies for youth with PBD (BD I, BD II, or BD not otherwise specified) as well as youth at risk of developing PBD.

The psychosocial treatments for PBD with the largest evidence base include Multi-Family Psychoeducational Psychotherapy (MF-PEP), Family-Focused Treatment for Adolescents (FFT-A), and Family-Focused Treatment adapted for youth at risk for bipolar disorder (FFT-HR). The core component of these interventions is providing family psychoeducation and skills building, and each is supported by at least one type 1 trial. Other psychosocial interventions that have shown encouraging treatment gains in preliminary research are supported by type 2 and type 3 studies. These include Individual-Family Psychoeducational Psychotherapy (IF-PEP), Child- and Family-Focused Cognitive-Behavioral Therapy (CFF-CBT), CBT for bipolar disorder in adolescents, Dialectical Behavior Therapy for Adolescents (DBT-A), and Interpersonal and Social Rhythm Therapy for Adolescents (IPSRT-A) (Fristad & MacPherson, 2013).

Multi-Family Psychoeducational Psychotherapy

Fristad and colleagues (2009) have developed and tested both individual and group formats of Psychoeducation-Based Psychotherapy (PEP) for school-aged children. PEP is an adjunctive, manualized intervention that combines psychoeducation with family therapy and CBT techniques. It is designed for children with bipolar or depression-spectrum disorders and their parents and focuses on educating the family on mood disorders; building symptom management skills, including emotion regulation, problem solving, and communication; and increasing support from other families and providers (Fristad, 2006). It was originally developed as an 8-session (90 minutes each) MF-PEP group for children and parents and has subsequently been adapted to a 24-session (50 minutes each) individual-family format (IF-PEP). Parents and children primarily attend sessions separately that run simultaneously during the course of treatment (Weinstein et al., 2013).

Fristad and colleagues (2003) conducted an initial RCT with 35 children (aged 8 to 11 years) with depression and PBD and their families to look at the effects of providing a six-session MF-PEP plus TAU ($N = 18$) compared with a waitlist control condition plus TAU ($N = 17$). At the 6-month follow-up, families who received MF-PEP reported increased perception of support from parents and peers, increased knowledge about mood symptoms, more positive family interactions as reported by the parents, and increased use of appropriate treatment services compared to those in the waitlist control condition. Changes in child mood severity symptoms were not significant after treatment in this study. Fristad and colleagues (2009) then conducted a larger type 1 RCT with 165 children (aged 8 to 12 years) with depression or PBD and their families, where participants were randomized to receive either eight 90-minute MF-PEP sessions plus TAU ($N = 78$) or the waitlist control condition plus TAU ($N = 87$). Participants were assessed at baseline and at 6, 12 and 18 months. Results indicated that MF-PEP was associated with a reduction in mood symptom severity compared to waitlist control over a 1-year follow-up as measured by a combination of the YMRS and CDRS-R scales. MF-PEP participants also demonstrated significant improvement in use of higher-quality mental health services, and this was mediated by parents' beliefs about treatment. As originally designed, this suggests that MF-PEP helped parents become better mental health consumers, and secondary data analyses showed that quality of services used also mediated treatment effects (Mendenhall et al., 2009).

MF-PEP was recently examined in another small open trial to study its implementation in a real-world setting such as a community outpatient clinic (MacPherson et al., 2014). In this trial, MF-PEP was offered to 40 children (aged 8 to 12 years) with depression or PBD and their families at two outpatient clinics, and it was delivered similarly as in the type 1 RCT described above. Preliminary findings indicate that MF-PEP was acceptable, feasible, cost-effective, and sustainable at these clinics. Parents also demonstrated significant improvement in knowledge of mood disorders at the end of treatment. This suggests that such psychosocial interventions for PBD may be transferable and effective in practice settings.

Family-Focused Treatment for Adolescents

FFT is a psychosocial intervention that was originally developed for adults with BD. Miklowitz and colleagues (2004, 2006, 2008) have adapted and evaluated FFT for adolescents with BD in several studies. FFT-A is designed for youth aged 12 to 17 years, and is delivered to youth and their families in 21 50-minute sessions over a 9-month period (Miklowitz et al., 2004). This treatment is based on understanding the central role of the family in managing a young person's PBD symptoms. It consists of four main stages: an *engagement* phase, where the goal is to connect with the patient and family and convey information about the treatment; a *psychoeducational* phase, which educates families on the nature, causes, and management of bipolar disorder (including providing tools for medication adherence and relapse prevention); *communication enhancement training*, where patients and families practice helpful speaking and listening skills; and *problem-solving skills training*, during which patients and families identify problems and generate and implement solutions that are mutually agreed upon (Miklowitz, 2012).

The efficacy of FFT-A as an adjunct treatment to pharmacotherapy for PBD has been established in a two-site type 1 RCT conducted by Miklowitz and colleagues (2008). In this trial, 58 adolescents (aged 12 to 17 years) with BPD and their families were randomized to receive either FFT-A plus pharmacotherapy

(*N* = 30) or enhanced care (three weekly family sessions focused on psychoeducation and relapse prevention) plus pharmacotherapy (*N* = 28). Patients and their families were assessed every three to six months for up to two years. Analyses were by intent to treat, and rates of completion did not differ between the two treatment arms. There were no significant group differences in rates of recovery from the index episode; however, patients receiving FFT-A had significantly shorter times to recovery from depression. The groups did not differ in time to recurrence of mania or depression, although FFT-A patients spent significantly fewer weeks in acute depressive episodes than those receiving enhanced care. FFT-A patients also had significantly greater reduction in depression severity scores and a more favorable trajectory of depressive symptoms over two years. These findings suggest that FFT-A as an adjunct treatment to pharmacotherapy might be effective in stabilizing bipolar depressive symptoms among adolescents, and may need to be supplemented with other interventions for mania symptoms to establish a complete recovery (Miklowitz et al., 2008).

Prior to this RCT, FFT-A was tested in several open trials that would meet criteria for type 3 studies. For example, Miklowitz and colleagues (2004) provided FFT-A in addition to pharmacotherapy to 20 adolescents (aged 13 to 17 years) with PBD. At the 12-month follow-up, they observed improvements in depressive and manic symptoms as reported by adolescents, and improvements in problem behaviors and internalizing and externalizing symptoms as reported by parents. While open trials such as this are not sufficient in and of themselves to establish the intervention's efficacy, they add to the growing body of literature and help inform type 1 studies as described above.

Family-Focused Treatment Adapted for Youth at High Risk for Pediatric Bipolar Disorder

Recently, FFT-A has also been adapted for children and adolescents at high risk for developing PBD (FFT-HR). Its possible efficacy has been established through one type 1 RCT (Miklowitz et al., 2013) and 1 type 3 open trial (Miklowitz et al., 2011). In these studies, youth were considered to be at high risk for developing PBD if they had been diagnosed with major depressive disorder, cyclothymic disorder, or BD not otherwise specified; had active mood symptoms in the past month; and had at least one first-degree relative with BD I or BD II. In the open trial, study clinicians delivered FFT-HR to 13 youth (aged 9 to 16 years) at risk for developing PBD and observed significant improvement in depressive symptoms, hypomanic symptoms and global functioning at the 12-month follow-up (Miklowitz et al., 2011). In the RCT, 40 high-risk youth (aged 9 to 17 years) were randomly assigned to receive either 12 sessions of FFT-HR or family education control (one or two family sessions that incorporated diagnostic feedback, mood monitoring, and symptom management skills) over a 4-month period. Youth and at least one parent were assessed at baseline and 4, 8, and 12 months after randomization. Intent-to-treat analyses demonstrated that youth in the FFT-HR group experienced more rapid recovery from initial mood symptoms, spent more weeks in remission, and had a more favorable trajectory of manic symptoms (as measured by their YMRS scores) over one year than youth in the family education control group. This suggests that FFT-HR may hasten and help sustain recovery from mood symptoms among youth at a high risk for PBD (Miklowitz et al., 2013). The effects of FFT-HR were more pronounced among youth in high-expressed-emotion families than in low-expressed-emotion families. The moderating effects of expressed emotion on patients' responses to FFT have been observed in other RCTs of adolescents and adults with BD (Kim & Miklowitz, 2004; Miklowitz et al., 2009), and therefore findings from this trial provide insight on subgroups of patients who might be more likely to respond to an early intervention such as FFT-HR.

Individual-Family Psychoeducational Psychotherapy

IF-PEP is a single-family adaptation of MF-PEP and has been examined in a small type 2 RCT with 20 children (aged 8 to 11 years) and their families (Fristad, 2006). This intervention consisted of 16 to 24 50-minute sessions alternating between the child and parent, and these sessions covered all the same content as in MF-PEP. IF-PEP also focused on coordination of school mental health services, sibling relationships, and healthy life habits such as good sleep hygiene, exercise, and nutrition. Researchers found that improvement in children's mood symptoms in the IF-PEP-plus-TAU arm was not significant when compared to the

waitlist-control-plus-TAU group; expressed emotion improved significantly more in IF-PEP-plus-TAU families than the waitlist-control-plus-TAU families; and there was no significant improvement in service utilization between the two treatment arms (Fristad, 2006). While this type 2 study offers some support for IF-PEP, additional research is needed to establish IF-PEP as an efficacious psychosocial intervention in the treatment of PBD.

Child- and Family-Focused Cognitive-Behavioral Therapy

CFF-CBT is a family-based adjunctive psychosocial treatment for children aged 7 to 13 years with PBD and their families. It integrates principles of family-focused treatment with those of CBT and interpersonal techniques and is a further adaptation of Miklowitz and Goldstein's FFT-A intervention to address the developmental needs of younger children and their families. Similar to FFT-A, it is based on a vulnerability-stress model, which suggests that environmental agents within the family, such as stressful life events, expressed emotion, coping, and negative communication styles, interact with an individual's genetic and biological predisposition to trigger illness (Pavuluri et al., 2004a). The CFF-CBT model is grounded in the neuroscience literature, specifically around dysfunction in neural systems responsible for processing and modulating emotions in PBD. As such, treatment aims to address impairments in affective circuitry and interpersonal functioning (Weinstein et al., 2013). Typically, CFF-CBT is a 12-session treatment that is delivered weekly over the course of three months (West et al., 2009). The acronym RAINBOW was formed to help parents and children remember the key components of this treatment: *Routine*, *Affect regulation*, *I can do it*, *No negative thoughts and live in the Now*, *Be a good friend and Balanced lifestyle for parents*, *Oh, how can we solve the problem*, *and Ways to get support* (West & Weinstein, 2012).

Findings from an open trial of CFF-CBT plus pharmacotherapy conducted with 34 youth (aged 5 to 17 years) with PBD and their families demonstrated the feasibility and acceptability of this intervention. Youth also experienced significant improvements in attention problems, aggression, mania psychosis, depression, and sleep disturbance and reported increased global functioning after treatment (Pavuluri et al., 2004a). Participation in the maintenance phase after the short-term intensive treatment phase of CFF-CBT was associated with being able to sustain symptom reduction and improvements in functioning over a 3-year period (West et al., 2007).

CFF-CBT has also been adapted to a multiple-family group format and assessed in an open trial where CFF-CBT group treatment was provided to 26 families who had children (aged 6 to 12 years) with PBD. Results indicated that this intervention was feasible and acceptable to families. It was further associated with significant improvement in the child's manic (but not depressive) symptoms and psychosocial functioning. Although not statistically significant, parents also reported increased knowledge and perceived ability to cope with their child's illness (Weinstein et al., 2013; West et al., 2009).

Results from these open CFF-CBT trials are promising, but more type 1 studies are needed to establish CFF-CBT's efficacy to treat PBD. An RCT of CFF-CBT is under way to assess the efficacy of CFF-CBT when compared with TAU in a sample of 60 children (aged 7 to 13 years) with PBD (Weinstein et al., 2012). Preliminary results suggest that CFF-CBT significantly improves symptoms of mania and depression compared to control TAU.

Cognitive-Behavioral Therapy for Bipolar Disorder in Adolescents

A manualized, adjunctive CBT intervention has also been developed for adolescents with PBD. It consists of 12 weekly sessions of acute-phase treatment (which includes sessions with both the child and the parent) followed by 6 to 10 biweekly sessions and biannual booster sessions. This intervention uses a traditional CBT framework with principles from CBT treatment for depressed adolescents, which are retargeted toward the specific needs of adolescents with PBD. Treatment usually involves psychoeducation, medication compliance, mood monitoring, problem solving, identifying and changing negative thinking patterns, sleep regulation, and family communication (Danielson et al., 2004).

Dialectical Behavior Therapy for Adolescents

DBT is an evidence-based intervention that is known to be efficacious in the treatment of adults

with borderline personality disorder (Linehan et al., 2006). Goldstein and colleagues (2007) have adapted this intervention to treat PBD since extreme emotion dysregulation is experienced by youth with PBD, and addressing this emotion dysregulation is a core component of DBT treatment (Birmaher et al., 2006). DBT-A for PBD is delivered in 36 sessions over the course of one year and involves both family skills training and individual psychotherapy for the youth. In a small open trial of DBT plus pharmacotherapy for 10 adolescents (aged 14 to 18 years) with PBD, researchers found that feasibility and acceptability of the intervention were high. Nine out of 10 patients completed treatment, 90% of scheduled sessions were attended, and parent and youth satisfaction rates were high. Adolescents demonstrated significant improvements in suicidality, emotion dysregulation, and depressive symptoms after treatment. There were no significant improvements in mania, interpersonal functioning, or number of medications prescribed (Goldstein et al., 2007).

Interpersonal and Social Rhythm Therapy for Adolescents

IPSRT is an empirically supportive adjunctive treatment for adults with BD (Frank et al., 2005) and has been adapted for youth with PBD (Hlastala and Frank, 2006). The adolescent program, IPSRT-A, comprises 16 to 18 sessions delivered over a period of 20 weeks. Most sessions are with the adolescent alone, with two or three family psychoeducational sessions (Hlastala & Frank, 2006). IPSRT-A differs from other psychosocial interventions for PBD in that it targets a biological diathesis for bipolar disorder—instability in circadian rhythms and neurotransmitter systems involved in regulation and social routines that affect circadian rhythms (Frank, 2005). Based on this, IPSRT focuses on stabilizing social and sleep routines as well as using interpersonal approaches to address psychosocial stressors that increase routine disruption (Hlastala & Frank, 2006). IPSRT has been examined in a small, open trial where 12 adolescents (aged 12 to 18 years) with PBD were treated with IPSRT over a 20-week period. Feasibility and acceptability of IPSRT-A were high; 11 out of 12 participants completed treatment and 97% of the treatment sessions were attended. IPSRT-A participants experienced significant improvements in mania, depression, general psychiatric symptoms, and global functioning. An RCT is under way to establish treatment efficacy (Hlastala et al., 2010).

CONCLUSION AND FUTURE DIRECTIONS

PBD is a severe and disabling condition that has seen higher rates of diagnosis and treatment over the past two decades. Despite the significant shift toward a better conceptualization of PBD, there remains a lack of data from type 1 RCTs to inform treatment recommendations. Much of the evidence for pharmacological and psychosocial treatments for PBD comes from type 2 and type 3 studies, which are limited by small sample sizes, low study completion rates, and lack of control groups and longitudinal data.

Currently, pharmacotherapy remains the first-line treatment for PBD. The two classes of medications currently used to treat PBD are mood stabilizers and SGAs. Of these, the FDA has approved lithium (for youth aged 12 and above), risperidone, aripiprazole, quetiapine (for youth aged 10 and above), and olanzapine (for youth aged 13 and above) for the treatment of PBD. The pharmacological literature on PBD provides empirical support for the efficacy of SGAs in treating acute manic or mixed episodes. However, the tolerability of these medications continues to be a challenge. Data from combination and head-to-head trials comparing SGAs to lithium or divalproex suggest that SGAs may be faster and more effective than mood stabilizers in treating manic symptoms during acute phases of treatment (Geller et al., 2012; Pavuluri et al., 2010). Additional placebo-controlled trials are necessary to support these findings.

At this time, there is limited information on the effectiveness of monotherapy with lithium or divalproex in managing acute manic symptoms. We hope to have additional information or recommendations on the use of lithium during acute treatment once the results from the Collaborative Lithium Trial (Findling et al., 2008a) become available. Data from combination trials suggest that monotherapy might be recommended for youth with mild to moderate PBD symptoms, but patients with more severe symptoms might benefit from combination

pharmacotherapy of an SGA with a mood stabilizer (Pavuluri et al., 2004b).

Treating bipolar depression continues to be a challenge for the pediatric population, with limited support from treatment studies of lithium and lamotrigine. Antidepressant monotherapy is discouraged due to the possibility of inducing mania. The current treatment guidelines recommend stabilizing mood before considering SSRIs to treat depressive symptoms (Kowatch et al., 2005); however, more placebo-controlled trials are needed to develop clear recommendations for treatment of bipolar depression. Similarly, when treating PBD comorbid with other conditions like ADHD, manic symptoms should be stabilized before initiating treatment with stimulants (Kowatch et al., 2005). Finally, there are limited data on continuation or maintenance treatment of PBD. Preliminary findings suggest that mood stabilizers may be more effective in maintenance treatment compared to SGAs, which have been associated with significant metabolic side effects (Correll, 2011; Findling et al., 2005; Pavuluri et al., 2009). More long-term studies are needed to investigate which medications best maintain gains from acute treatment and inhibit or prolong time to relapse.

Over the past decade, considerable progress has also been made in the development and evaluation of psychosocial interventions to treat PBD. Currently, the three psychosocial interventions that are the most thoroughly examined and supported by at least one type 1 RCT are MF-PEP (Fristad et al., 2009), FFT-A (Miklowitz et al., 2008), and FFT-HR (Miklowitz et al., 2013). These interventions focus on family psychoeducation plus skills building and are likely to be the most efficacious as adjunctive treatments to pharmacotherapy for PBD. At the next level, IF-PEP is supported by one type 2 RCT. CFF-CBT and CBT for BD in adolescents are supported by three type 3 studies. DBT-A and IPSRT-A would currently still be considered experimental for the treatment of PBD since they are each supported by only one type 3 open trial. Several RCTs are under way to evaluate the efficacy of these interventions with more rigor.

Although results from the reviewed psychosocial trials are promising, it is important to note some limitations that affect the generalizability and interpretation of the reported findings. First, except for the type 1 RCTs, most samples were small and composed mainly of white males, which makes it challenging to draw broader conclusions about these treatments. Second, all studies included youth with a range of bipolar disorders with varying levels of symptom severity, and in some cases even depressive disorders. This limits our ability to attribute treatment response entirely to the intervention or to determine which of these treatments work best for certain subsets of the PBD population. Another major methodological limitation is the use of waitlist control conditions or other enhanced care conditions in the RCTs instead of a psychological placebo or other active treatment. As a result, one cannot rule out the possibility that significant changes were due to other factors not related to the treatment interventions. Other limitations include all studies being conducted in university-based settings or specialty outpatient clinics, all trials allowing for continuation of TAU or pharmacotherapy without being controlled or reported, and most trials including carefully managed pharmacotherapy by highly trained psychiatrists that might have had a positive effect on treatment outcomes (Fristad & MacPherson, 2013).

Despite these limitations, preliminary findings on pharmacological and psychosocial treatments for youth with PBD are promising and have important clinical implications. More rigorous RCTs are needed with diverse samples that compare these interventions to placebo or other active treatments and clarify whether they are safe and effective in the long term. Additional research should also examine moderators of treatment response, approaches for early intervention, and the effectiveness and implementation of empirically supported treatments in community-based practice settings.

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10

Psychosocial Treatments for Bipolar Disorder

Anjana Muralidharan
David J. Miklowitz
W. Edward Craighead

Although pharmacological interventions remain the primary treatment for bipolar disorder (BD), adjunctive psychosocial interventions have the potential to increase adherence to medication regimens, decrease hospitalizations and relapses, decrease severity of symptoms, improve quality of life, and enhance mechanisms for coping with stress. Four type 1 and 2 studies have established that group psychoeducation, designed to provide information to BD patients about the disorder and its treatment, leads to lower rates of recurrence and greater adherence to medication among remitted BD patients at both short- and long-term follow-up. Type 1 and 2 studies that evaluated cognitive-behavioral therapy (CBT) as an ancillary treatment have found mixed results but generally supportive evidence indicating that the intervention is useful in preventing relapse to depression in remitted patients. Three type 1 studies have shown that family-based intervention, such as Family-Focused Therapy (FFT), may be effectively combined with pharmacotherapy to reduce recurrences and hospitalization rates in adult patients. A type 1 trial with acutely depressed BD patients comparing CBT, FFT, and Interpersonal and Social Rhythm Therapy (IPSRT) to a short-term psychoeducational intervention reported that the three intensive psychotherapy conditions were associated with higher rates of and faster times to recovery. Finally, three type 1 studies have indicated that family psychoeducation and skills training may be effective adjuncts to pharmacotherapy for bipolar spectrum children and adolescents and youths at high risk for BD. Further investigation into mechanisms of treatment efficacy and moderators of clinical outcome will inform continued development and dissemination of effective psychosocial interventions for BD.

INTRODUCTION

Up to 4% of the adult population in the United States experiences BD (Kessler, Berglund, Demler, Jin, & Walters, 2005). For more than 90% of those patients, the disorder is characterized by a recurrent course of mood fluctuation over the lifetime (American Psychiatric Association [APA], 2013). Several studies indicate that approximately half of these patients experience lengthy periods of interepisode residual symptoms despite pharmacotherapy (e.g., Judd et al., 2002; Solomon et al., 2010). BD has been listed as the sixth leading cause of disability among the physical and psychiatric disorders (Murray & Lopez, 1996), and recent epidemiological data indicate that BD continues to be a significant contributor to global disease burden (Whiteford et al., 2013).

BD has a strong impact on patients' work and social functioning. The majority of individuals with BD experience significant work impairment between episodes (Goetz et al., 2007); in a nationally representative U.S. sample, BD was associated with 65.5 lost workdays per patient per year (Kessler et al., 2006). Stable outpatients with BD exhibit social functioning deficits similar to stable outpatients with schizophrenia (Dickerson et al., 2001). The effects of manic episodes on social, occupational, and family functioning can be observed 5 years later (Coryell et al., 1993). The risk of suicide in BD patients is at least 15 times that for the normal population (APA, 2013). Unfortunately, despite recent advances in the treatment of this debilitating disorder, it is estimated that between one fourth and nearly two thirds of BD patients have never sought treatment (Goodwin & Jamison, 2007).

In the recently published fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*-5), bipolar spectrum disorders have been separated from depressive disorders and placed in their own category. This is in acknowledgment of the distinction of this class of disorders from unipolar depression, and its overlap in terms of genetic risk with psychotic spectrum disorders and schizophrenia (APA, 2013). Bipolar spectrum disorders are distinguished from other classes of disorders by the presence of manic or hypomanic symptoms. To meet criteria for bipolar I or II disorder, individuals must exhibit a distinct period of euphoric/elevated mood and/or irritable mood. In *DSM-5*, these mood changes must be accompanied by increased energy and/or goal-directed activity to meet criteria for a manic or hypomanic episode. The majority of individuals with a bipolar illness—although not all—suffer from depressive episodes. Bipolar depression may be distinct from unipolar depression in terms of younger age of onset, greater frequency of episodes, and greater short-term mood variability (Cuellar et al, 2005). Thus, despite overlap of symptoms with other mental illness categories, bipolar spectrum disorders have a number of unique features that warrant specialized, disorder-specific treatment.

A common etiological explanation for BD points to biological dysregulation (with a major genetic component) that is either activated or maintained by psychosocial stressors such as negative family environments or significant life events (e.g., Alloy et al., 2009; Miklowitz & Johnson, 2006). Because of the biological dysregulation associated with BD, pharmacological treatments have become the primary focus of intervention. Although the atypical antipsychotic medications are increasingly treatments of choice for acute manic episodes, lithium carbonate and anticonvulsants such as lamotrigine remain the most effective interventions and figure prominently in the treatment of acute depression and longer-term maintenance treatment (Malhi et al., 2009; Tohen & Vieta, 2009). With one or more of these medications, the majority of patients can now experience some level of mood stabilization with continued use.

Within the context of pharmacological interventions as the primary treatment for BD, psychosocial interventions have been designed to increase adherence to medication regimens, reduce the number of hospitalizations and relapses, decrease severity of symptoms, diminish the impact of stress, and improve patients' quality of life. The major components of a multifaceted psychosocial treatment program could include individual or group psychoeducation (with special attention to medication adherence and symptom management), cognitive training, individual cognitive-behavioral or interpersonal therapy, and family therapy. In this chapter we review the empirical outcome data for each of these treatment components.

PSYCHOEDUCATION

BD patients frequently express resentment at how little information they have received about their disorder or their medications (Goodwin & Jamison, 2007). The primary focus of psychoeducation is provision of information regarding the multifaceted nature of the disorder and its successful treatment. The issue of medication adherence is a particularly salient aspect of the education and treatment of BD. In fact, poor adherence to medication is a highly significant predictor of poor treatment response in BD (Goodwin & Jamison, 2007). Despite the high risk of relapse due to nonadherence, more than half of patients with BD on mood stabilizers or atypical antipsychotics choose to discontinue their medication or do not take it as prescribed (Arvilommi et al., 2013). Therefore, enhancing medication adherence is an important goal of ancillary psychosocial treatments.

Early Psychoeducational Studies

Early attempts to enhance medication adherence in psychiatric patients included brief psychoeducational interventions, tested in type 2 or 3 trials. Interventions including a series of psychoeducational lectures (Seltzer, Roncari, & Garfinkel, 1980) or a brief educational video accompanied by informational handouts (Harvey & Peet, 1991) were found to have favorable short-term effects on knowledge about BD, self-reported medication adherence, and/or plasma lithium levels.

In a type 1 trial that improved on these early efforts by including a more tightly controlled experimental design and a longer period of follow-up, Perry, Tarrier, Morriss, McCarthy, and Limb (1999) compared patients who received medication management with patients who received medication management and a 7- to 12-session individual psychoeducation intervention (n = 69). The psychoeducation consisted of sessions to teach patients to recognize emergent symptoms of BD and to seek appropriate medical/preventive interventions. During an 18-month follow-up period, manic relapses were significantly delayed among bipolar patients in the psychoeducation versus the medication-only group; no differences were found in survival times prior to depressive relapses. Psychoeducation also had a stronger impact on social and occupational functioning than did medication management. There were no differences between the groups in medication adherence.

Group Psychoeducation

A number of studies suggest that group psychoeducation is an effective adjunct to pharmacotherapy for individuals with BD in remission. One type 1 study randomized 84 participants to receive a 12-session group-based psychoeducation intervention or treatment as usual; the psychoeducation group exhibited reduced rates of relapse of any type over the 1-year follow-up period (Castle et al., 2010). Three type 1 and 2 studies show both positive (D'Souza et al., 2010; Eker & Harkin, 2012) and negative (de Barros Pellegrinelli et al., 2012) results. Differences in intervention length, topics covered, and treatment settings may account for these discrepant findings.

Investigators at the Bipolar Disorders Program of Barcelona conducted a rigorous study of a group psychoeducation intervention. This type 1 randomized trial (n = 120 remitted patients with BD; Colom et al., 2003) had an active control condition that matched the experimental group in terms of amount of clinical contact: One group of patients received psychopharmacology and 21 weekly sessions of group psychoeducation, and another received psychopharmacology and 21 unstructured, nondidactic group support sessions. The experimental group psychoeducation focused on illness management (e.g., relapse prevention planning) and decreasing the stigma of mental illness. Patients had been in remission for at least 6 months prior to entering the trial. At the end of 2 years, the rate of relapse was 67% in group psychoeducation and 92% in the unstructured groups. Patients in the experimental group also had higher and more stable lithium levels (Colom et al., 2005). A 5-year follow-up of this study sample indicated that gains from the intervention were maintained. Over the follow-up period, the experimental group reported greater time to recurrence, fewer recurrences, fewer days hospitalized, and less time acutely ill than the control group (Colom et al., 2009).

In an effort to independently replicate Colom and colleagues' (2003) findings, a type 2 study conducted at two outpatient mental health clinics in Italy used their full 21-session intervention. Patients in the psychoeducational groups exhibited decreased rates of hospitalization and fewer days hospitalized than patients in the control group. However, this study did not use an active control intervention (Candini et al., 2013). Thus, independent replication of Colom and colleagues' findings is warranted in a large, type 1 study with an active control condition; one such trial is under way (Morriss et al., 2011).

Overall, group psychoeducation appears to be an effective adjunct to pharmacotherapy for BD patients in remission. Evidence from several type 1 and 2 studies indicates that this intervention is associated with increased medication adherence, increased time to relapse, decreased severity of symptoms, and decreased time spent ill. Group psychoeducation may be particularly helpful in preventing manic relapse, perhaps by improving medication adherence and/or the ability to detect and intervene with prodromal manic symptoms. Questions remain regarding what specific components of group psychoeducation are essential for efficacy. For example, it is unclear whether the intervention must be a specific length or cover certain topic areas in order to be efficacious. Future

studies examining mediators and moderators of outcome, as well as dismantling studies aimed at identifying the "active ingredients" of the intervention, could help to address these questions.

Group Psychoeducation Within Systems of Care Models

Two type 1 studies examined psychoeducation groups embedded within larger systems of care. First, a large-scale randomized controlled trial (RCT) at a health maintenance organization examined group psychoeducation within the context of a multicomponent care-management intervention (Simon et al., 2005). Patients (n = 441) had all been treated within a managed care network within the prior year. They were randomly assigned to pharmacotherapy alone or to a care-management program consisting of pharmacotherapy, telephone-based monitoring, care planning within an interdisciplinary team, and group psychoeducation. The group psychoeducation model focused on individual life goal setting (Bauer & McBride, 1996). Over a 2-year follow-up, patients in the program had lower mania scores and spent less time hypomanic or manic than those who received pharmacotherapy alone (Simon, Ludman, Bauer, Unutzer, & Operskalski, 2006). The intervention did not differentially affect depressive symptoms.

Second, a type I study conducted at 11 Veterans Affairs hospitals across the United States examined group psychoeducation for BD within a collaborative model of chronic care. This model included group psychoeducation, patient monitoring by a nurse care manager, and monitoring of physician adherence to treatment guidelines. Participants (n = 306) were randomized to 3 years in the intervention or usual care. The intervention significantly reduced time spent in affective episodes, especially mania, over the 3 years. Participants in the intervention showed significant improvements on measures of social functioning, quality of life, and treatment satisfaction. The intervention was cost-neutral (Bauer et al., 2006).

COGNITIVE REMEDIATION

Individuals with BD exhibit significant cognitive impairment, both during and between mood episodes (Henin et al., 2009). A novel treatment for BD, cognitive remediation (CR), emphasizes strategies to improve attention, concentration, and memory. CR has also been found to be useful in improving cognitive impairment in schizophrenia spectrum disorders (Wykes et al., 2011). Two type 3 studies and one type 1 study examined CR in samples of patients with BD. In the first study (open trial; n = 18), individuals with BD participated in 14 sessions of individual CR. Subjects exhibited improvements in depressive symptoms and occupational functioning at the end of treatment and at the 3-month follow-up (Deckersbach et al., 2010). In the second type 3 study, 51 patients with unipolar and bipolar depression demonstrated improvements in working memory after 10 weeks of CR (Meusel et al., 2013).

A type 1 study examined an intervention termed "functional remediation," which combined CR with a focus on improving psychosocial functioning through psychoeducation about the nature and impact of cognitive impairment; this intervention was compared to general psychoeducation and treatment as usual in 239 subjects with BD (Torrent et al., 2013). At the end of treatment, functional remediation was associated with greater improvement in global psychosocial functioning compared to treatment as usual; there were no significant differences in psychosocial functioning between the functional remediation and general psychoeducation conditions. Functional remediation did not lead to improved mood symptoms.

The long-term impact of CR on cognition and psychosocial functioning in BD remains to be determined. Given the growing support for the use of CR in psychotic spectrum disorders, additional RCTs in BD appear to be warranted.

INDIVIDUAL PSYCHOTHERAPY INTERVENTIONS

Cognitive-Behavioral Therapy

The past 15 years have seen increased interest in the addition of individual CBT to mood-stabilizing medication regimens for the treatment of BD. The primary assumption of CBT is that mood swings are in part a function of negative thinking patterns (both self-statements and core dysfunctional schemata) that can be alleviated by a combination of behavioral activation and cognitive restructuring

strategies to increase the patient's engagement with the environment.

A large-scale (n = 103) type 1 randomized study (Lam et al., 2003; Lam, Hayward, Watkins, Wright, & Sham, 2005) compared CBT (average of 14 sessions plus 2 booster sessions over 12 months) with pharmacotherapy versus a control group (usual care) with pharmacotherapy. Patients had been in remission for at least 6 months but were considered prone to relapse because they had had at least three episodes in the past 5 years. The results suggested a short-term advantage for CBT: at 1 year, the relapse rate in the CBT condition was 44% and in the control condition it was 75%. Patients in CBT also had higher social functioning and were better able to cope with manic prodromes. In an 18-month follow-up after the initial 1-year study, patients in CBT and usual care did not differ in relapse rates. However, CBT continued to be associated with better self-reported mood and fewer days spent in episodes. A secondary analysis of data from this trial found that BD patients with a hyper-positive sense of self at baseline were more likely to relapse during therapy (Lam et al., 2005).

The largest type 1 CBT trial to date was conducted in the United Kingdom (Scott et al., 2006). Patients (n = 253) were recruited from five different sites in a variety of clinical states. Patients were randomly assigned to CBT plus medications (22 sessions) or treatment as usual and medications. No differences emerged between CBT and treatment as usual on time to recurrence. The authors reported a treatment by prior episodes interaction (CBT was associated with longer survival times prior to recurrences in patients with fewer than 12 prior episodes, whereas treatment as usual was associated with longer survival among patients with 12 or more prior episodes). However, a type 4 study (a "meta-regression" of six RCTs) found no relationship between risk for relapse and number of prior episodes (Lam, Burbeck, Wright, & Pilling, 2009).

An adaptation of CBT, schema-focused CBT, which uses imagery and reliving of early life experiences to target negative cognitive schema, was tested in a type 1 study (Ball et al., 2006). Fifty-two patients with BD on pharmacotherapy were randomized to schema-focused CBT or treatment as usual for 6 months. The schema-focused CBT group had lower levels of depression symptoms and dysfunctional attitudes than the treatment as usual group at the end of treatment. At the 18-month follow-up, the schema-focused CBT group exhibited higher scores on a clinical global impression scale.

A type 2 study investigated whether CBT combined with psychoeducation had a greater impact than psychoeducation alone. Patients with BD in full or partial remission (n = 79) completed 7 sessions of individual psychoeducation; following these sessions, half the sample was randomized to complete a 13-session CBT protocol (Zaretsky et al., 2008). Rates of relapse, hospitalization, and adherence, and levels of manic symptoms, were not different between groups. Participants who received CBT had lower depression scores and dysfunctional attitudes. Data from this study, along with the findings from the study by Ball and colleagues (2006), suggest that CBT may have a particular impact on depression symptoms, and that improvement in dysfunctional negative attitudes may mediate this effect.

All of these studies compared CBT to treatment as usual. More recently, researchers have compared CBT to active control conditions, a more rigorous test of efficacy. For example, Meyer and Hautzinger (2012) compared individual CBT to supportive therapy in a sample of 76 patients with BD in remission. Both interventions included 20 sessions delivered over 9 months. No significant differences in change in depression or mania symptoms between the treatment conditions were found at the end of treatment. Participants were followed for 2 years after treatment and, through the entire 33-month study period, no differences in relapse rates between treatment groups were seen.

Another type 1 study compared CBT to group psychoeducation, randomizing 204 participants with BD who were in remission or minimally symptomatic to receive 6 sessions of group psychoeducation or 20 sessions of individual CBT (Parikh et al., 2012). Despite the greater length of treatment and individualized format of CBT, there were no significant differences between groups in terms of risk for relapse or levels of mania or depression symptoms over 18 months of follow-up. These results suggest that group psychoeducation may be a more cost-effective approach to the psychosocial treatment of BD than individual CBT.

CBT has been rigorously studied in a number of type 1 and 2 trials. Overall, evidence for the efficacy of CBT for BD is mixed. One type 1 study suggests that CBT decreases risk for relapse in the short term (Lam et al., 2005); whether this decreased risk is maintained over long-term follow-up is unclear. Two

studies suggest that the treatment may be particularly impactful in preventing depression in remitted BD patients, potentially through cognitive restructuring of dysfunctional negative attitudes (Ball et al., 2006; Zaretsky et al., 2008). Also, three type 1 studies, including two that employed an active control condition (Meyer & Hautzinger 2012; Parikh et al., 2012; Scott et al., 2006), did not find any significant additive impact of CBT. Further inquiry into the mechanisms of action of CBT treatments or potential moderators of treatment response could help to answer whether and in what circumstances CBT is an effective adjunct to pharmacotherapy for patients with BD.

Interpersonal and Social Rhythm Therapy

Interpersonal Psychotherapy (IPT; Weissman, Markowitz, & Klerman, 2000) is an individual therapy that was originally developed as a treatment for major depressive disorder. Based on modifications of IPT, IPSRT, developed by Frank and her colleagues (Frank, Swartz, & Kupfer, 2000), is an adjunctive individual therapy for BD. IPSRT is based on the social rhythm stability hypothesis (Ehlers, Frank, & Kupfer, 1988). IPSRT has two goals: (a) to help patients to understand and renegotiate the social context associated with mood disorder symptoms and (b) to encourage patients to recognize the impact of interpersonal events on their social and circadian rhythms, and to regularize these rhythms to gain control over their mood cycling. Like other psychosocial therapies, IPSRT includes education about BD and strategies for improving drug adherence (Frank, Kupfer, Ehlers, & Monk, 1994).

The Western Psychiatric Institute at the University of Pittsburgh Medical Center conducted an initial controlled type 1 trial of IPSRT that included lithium and other mood stabilizers (Frank et al., 1997, 2005). Patients were assigned to IPSRT or to a comparison individual therapy, intensive clinical management, which consisted of 20-minute weekly sessions focused on symptom management and medication adherence. Randomization occurred at two time points: (1) initiation of acute stabilization and (2) initiation of maintenance prevention. No differences were found between IPSRT and the intensive clinical management treatment strategies in time to stabilization of the acute episode (Frank et al., 1997). However, patients assigned to IPSRT in the acute phase showed greater stabilization of their daily routines and sleep/wake cycles, and a lower likelihood of recurrence during the maintenance phase. Patients assigned to IPSRT in the acute phase also survived longer without a mood disorder recurrence in the maintenance treatment phase, even if they were not assigned to IPSRT in the maintenance phase (Frank et al., 2005). The presence of a comorbid anxiety disorder moderated this effect; individuals with this comorbid condition had shorter times to recurrence when they were assigned to IPSRT in the acute phase. IPSRT also had a positive impact on vocational functioning (Frank et al., 2008). Future trials of IPSRT would benefit from the use of a control condition that is matched to IPSRT in terms of amount of therapist contact, and/or from comparison to an established intervention such as group psychoeducation.

FAMILY-BASED INTERVENTIONS

BD cycling affects and is affected by the family context (Miklowitz, 2004). Just as the patient needs to understand the disorder and its treatment, the patient's parents, siblings, spouse, and/or other family members need to learn skills to cope with the disorder's impact on interpersonal interactions and relationships.

Current approaches to family treatment are psychoeducational, meaning that the intervention provides patients and their families information about the disorder and training in the coping strategies and interpersonal skills necessary for dealing with the disorder. Psychoeducational family interventions are designed to teach the patient and close relatives (typically spouse or parents) about the symptoms, course, and treatment of BD, emphasizing strategies for relapse prevention. Psychoeducational family interventions are most successful when accompanied by pharmacotherapy (typically mood-stabilizing medications, with or without adjunctive agents).

Family Environment and Bipolar Disorder

The nature and extent of stress in the family environment predict the course of BD. Much of the literature examining family environment in BD uses a construct termed expressed emotion (EE; Miklowitz, 2007). High EE, characterized by criticism and hostility from or emotional overinvolvement (intrusiveness)

in a caregiver or family member, predicts a poorer course of illness in a number of psychiatric disorders, including schizophrenia, depression, eating disorders, and BD (Hooley, 2007). Specifically, individuals with BD who return to high-EE families following hospitalization have a two to three times greater risk of relapse in the ensuing 9 months than patients who return to low-EE families (Barrowclough & Hooley, 2003; Miklowitz, 2004). EE appears to contribute to a poorer course of illness in BD beyond its correlation with genetic loading or symptom severity (Miklowitz, 2004). Thus, the family environment plays a strong prognostic role in mood disorders (see also the meta-analysis by Butzlaff & Hooley, 1998).

On the positive side, BD patients with high levels of social and emotional support from friends and families recover more quickly from a bipolar episode than patients with low levels of such support (Johnson, Winett, Meyer, Greenhouse, & Miller, 1999). Thus, family interventions that maximize the protective effects of the family context are potentially powerful adjuncts to pharmacotherapy in relapse prevention.

The Cornell University and Brown University Studies

Several investigations have examined whether family interventions, as adjunctive to pharmacotherapy, lead to improved outcomes in BD. To this end, a group at the Cornell University Medical College developed and tested an inpatient family intervention for families of hospitalized psychiatric (including BD) patients, focused on helping participants cope with the hospitalization and make plans for a positive adjustment after discharge. The intervention was associated with better symptomatic and global functioning at the 6- and 18-month follow-ups (Clarkin et al., 1990).

Clarkin, Carpenter, Hull, Wilner, and Glick (1998) later conducted a type 2 study specifically for BD: a marital intervention focused on psychoeducation about the disorder and improving spousal communication, as an adjunct to standard medications. When compared to standard medications only, the marital intervention did not yield significant improvements in mood symptoms or time to recurrence over the 11-month treatment period; however, it was associated with greater improvements in global functioning and higher levels of medication adherence over the treatment period.

In a type 1 trial, Miller, Solomon, Ryan, and Keitner (2004) at Brown University Medical Center assigned 92 bipolar patients who were either manic or depressed to one of three treatment conditions: (a) standard treatment, consisting of medication plus active clinical management by a psychiatrist; (b) standard treatment plus family therapy (six to eight sessions over 4 months of treatment, and follow-up "booster sessions"); and (c) standard treatment plus multifamily groups, in which four to six families met together in 1½-hour sessions over 6 weeks, followed by "reunion meetings" over the next 6 months. The family treatments were oriented toward education about the disorder and problem solving. Results indicated that the two family-treated groups did not differ from the standard care group in time to recovery or number recovered. Family intervention did not hasten the stabilization that would be expected from pharmacotherapy alone. However, family impairment was a significant moderator of outcomes in this trial: For families with high levels of impairment, the addition of family intervention (therapy or psychoeducation) resulted in significantly fewer depressive episodes and decreased time spent depressed (Miller et al., 2008).

A secondary analysis of these data examined the 53 patients who recovered from their index mood episode during the study to investigate the potential effect of treatment on risk for recurrence. Treatment groups did not differ on rates of recurrence, time to recurrence, or time to hospitalization over the 28-month follow-up period. However, participants in the adjunctive multifamily groups required significantly fewer hospitalizations than the other two groups (Solomon et al., 2008).

Family-Focused Treatment

Miklowitz and Goldstein (1990, 1997) developed a 9-month FFT program for bipolar adults who had been recently hospitalized or were being treated on an outpatient basis for a recent acute episode. FFT is delivered in 21 sessions titrated over 9 months (12 weekly, 6 biweekly, and 3 monthly). The model is similar to Falloon, Boyd, and McGill's (1984) behavioral family management for schizophrenic disorders, but it is adapted to the needs of BD patients and their families.

The treatment model comprises three modules. In the first module, psychoeducation, patients and

relatives are given information about how to cope with BD. This includes didactic material about the symptoms, diagnosis, causes, and prognosis of the disorder; vulnerability and stress interactions; and risk and protective factors. It also includes a relapse prevention drill in which participants identify the patient's prodromal signs of mania or depression and the family develops plans for how to intervene should these appear (e.g., arranging an emergency medical visit or hospitalization). Later modules of FFT (communication enhancement training and problem-solving skills training) involve teaching the patients and family members the skills for dealing with disorder-related conflicts; this is accomplished by role playing and behavioral rehearsal assignments. A type 3 pilot study (Miklowitz & Goldstein, 1990) compared 9 BD patients and their families to 23 historical controls who did not receive FFT; relapse rates over 9 months were 11% (1/9) in FFT versus 61% (14/23) in the historical controls.

Miklowitz, George, Richards, Simoneau, and Suddath (2003a) at the University of Colorado reported the results of a type 1 clinical trial of FFT. Bipolar I patients (n = 101) were randomized to FFT (9 months, 21 sessions) or a brief psychoeducation comparison condition called crisis management, consisting of two sessions of family education followed by 9 months of crisis intervention, delivered on an as-needed basis. All patients received standard pharmacotherapy from community psychiatrists. Survival analyses indicated that patients in FFT and pharmacotherapy had higher 2-year survival rates without relapsing (52%) and longer survival times during the 2-year study than patients in the crisis management plus pharmacotherapy group (17%). Patients in FFT stabilized more completely over 2 years in terms of depressive symptoms and, to a lesser but still significant extent, manic symptoms. Moreover, patients in FFT had higher rates of medication adherence over the 2-year study. Improvements in medication adherence mediated the effects of FFT on manic, but not depressive, symptoms.

Within the Colorado trial, Simoneau, Miklowitz, Richards, Saleem, and George (1999) examined whether FFT leads to improvements in the quality of family communication and problem-solving skills. They coded videotapes and transcripts of problem-solving interactions from a subset of families assessed before and after the 9-month FFT or CM protocols (n = 44). No differential effects were found for treatments in reducing the frequency of negative communication behaviors (i.e., criticisms, disagreements, negative nonverbal behaviors) among patients and family members. Within the FFT group, however, positive communication behaviors among patients and relatives increased from the pretreatment to the posttreatment period. When the family was not treated (the crisis management condition), positive communication decreased slightly over the pretreatment to the posttreatment period. Moreover, treatment-associated increases in positive interactional behaviors (particularly patients' nonverbal behaviors) predicted greater improvement over the study year in patients' mood disorder—notably depressive—symptoms. Thus, FFT may achieve its effects in part through increasing the protective influences of the family environment.

In addition to the Colorado trial, FFT was tested in conjunction with IPSRT in an open trial with a historical comparison group (Miklowitz et al., 2003b). Patients (n = 30) who received an average of 30 individual IPSRT and family psychoeducational sessions (with parents or spouses) had longer survival times prior to depressive relapse and greater stabilization of depressive symptoms over 1 year than patients (n = 70) who received pharmacotherapy, two sessions of family psychoeducation, and crisis intervention as needed.

The Colorado study compared FFT to a brief psychoeducational comparison group that was not matched on amount of therapist attention. In a subsequent randomized type 1 trial, Rea and colleagues (2003) at the University of California, Los Angeles, compared 9 months of clinic-based FFT to an individually focused therapy. BD patients began the study during a hospitalized manic episode (n = 53) and were maintained on mood-stabilizing medications. Patients in individually focused therapy received regular sessions of education, support, and problem solving, with a duration and pacing of sessions that was identical to FFT (21 weekly, biweekly, and monthly sessions). Patients in the FFT group had longer delays prior to relapse, but only when the full 2- to 3-year study period was considered. Patients who received FFT also had a lower risk of rehospitalization (12%) than patients in individual therapy (60%) during a 1- to 2-year posttreatment interval. No group differences were observed in the first year, suggesting that for some patients and families, the effects of FFT may not be "absorbed" until the full course of treatment is

complete. Of particular significance for health care cost containment is that patients in FFT were less likely to be hospitalized when they did relapse than were the individually treated patients. Thus, FFT appears to have assisted patients and families in avoiding a hospitalization when a relapse occurred.

Caregiver Psychoeducation

Three studies have examined the efficacy of "caregiver only" psychoeducational groups. A type 3 study (van Gent & Zwart, 1991) examined the effects of educating the partners of BD patients. Subjects were 26 manic bipolar patients and their partners: 14 partners attended psychoeducation sessions without their patient-partners being present, and the partners of the 12 remaining patients served as controls. After the intervention and at a 6-month follow-up, partners who attended psychoeducational sessions demonstrated a greater knowledge of the disorder, medications, social support, and coping strategies. However, patients' medication adherence did not change over the 12-month follow-up, compared with the preintervention values or the control group values.

A type 1 controlled trial randomized caregivers for 113 euthymic medicated BD patients to receive 12 group psychoeducation sessions or no intervention. Caregivers in the psychoeducational groups received information about BD and training in coping skills. Patients were assessed monthly during the treatment period and over a 12-month follow-up; those with caregivers in the psychoeducation group exhibited decreased risk for any mood recurrence. When manic and depressive episodes were analyzed separately, patients with caregivers in the psychoeducation group exhibited greater time to manic recurrence and decreased risk for manic recurrence; this was not the case for depressive recurrences (Reinares et al., 2008). A post hoc analysis of these data found that the positive effects of the intervention on time to recurrence only held true for recently diagnosed individuals and not others (Reinares et al., 2010).

A type 2 study examined an adaptation of FFT designed to promote healthy behaviors and self-care in caregivers of patients with BD: Family-Focused Treatment-Health Promoting Intervention (FFT-HPI: Perlick et al., 2010). FFT-HPI is a 12-session individual intervention that includes skills training to help caregivers better manage distress related to caregiving and engage in health-promoting behaviors. Forty-six primary caregivers for individuals with BD were randomized to FFT-HPI or an 8- to 12-session health education intervention delivered by videotape. Compared to the control group, FFT-HPI was associated with greater decreases in patient depression at the end of treatment; this relationship was mediated by decreases in caregiver depression.

Summary of Findings on Family-Based Interventions

In summary, three type 1 studies support the efficacy of family-based intervention for the treatment of BD patients stabilizing from an acute episode, including one trial that used a control condition that matched the experimental condition in terms of amount of clinician contact. One type 1 study supports the efficacy of caregiver psychoeducation in the treatment of euthymic BD patients. Family-based interventions appear to decrease rates of hospitalization, decrease risk for relapse, and increase time to relapse in treated patients. Future trials of family-based interventions would benefit from comparison to a strong control condition with sessions of equal number and duration as the intervention being tested. Family-based interventions such as FFT should also be compared to other evidence-based interventions, such as group psychoeducation, to more rigorously test the unique impact of family involvement.

THE SYSTEMATIC TREATMENT ENHANCEMENT PROGRAM FOR BIPOLAR DISORDER

To examine the efficacy of adjunctive psychosocial intervention in combination with mood stabilizers, a large multisite type 1 trial was conducted as part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD; Miklowitz et al., 2007). Currently depressed patients with BD ($n = 293$) all received mood-stabilizing medications; they were then randomized to receive a standard antidepressant agent or a placebo. Patients were further randomized to one of four psychosocial intervention conditions: a 3-session psychoeducational intervention or 30 sessions of one of three intensive psychotherapies (FFT, CBT, or IPSRT). Patients

assigned to any intensive psychotherapy had higher rates of recovery (64.4% vs. 51.5%) at the end of the study year and recovered 110 days faster on average. Also, patients in intensive psychotherapy were more likely to be clinically well in a given month over the course of the study (Miklowitz et al., 2007). Psychotherapy appears to be an essential component of the treatment of bipolar depression.

Importantly, patients randomized to adjunctive antidepressants were not significantly different from patients randomized to adjunctive placebo in terms of speed of recovery from depression (Sachs et al., 2007). When clinicians treat bipolar depressed patients with mood-stabilizing medication, adding an intensive therapy may be associated with more rapid recovery than adding an antidepressant (Miklowitz et al., 2007). There were no significant differences among the intensive psychotherapies; thus, it may be that common factors across these interventions contribute to improved clinical outcomes. Potential common factors include therapeutic alliance with a mental health professional, identification of prodromal symptoms, mood management and relapse prevention strategies, focus on medication compliance, and interpersonal and family relationship repair.

Investigators have examined potential moderators of response to psychotherapy using data from STEP-BD. In one naturalistic study of acutely depressed BD patients (n = 248; not the RCT sample), patients who were more severely depressed and functionally impaired benefited most from intensive adjunctive psychotherapy, whereas patients who were less severely ill and impaired benefited most from less frequent contacts (i.e., maintenance check-ins; Miklowitz et al., 2006b). Another study (n = 269) found that within the RCT sample, intensive psychotherapy was more effective for individuals with a lifetime comorbid anxiety disorder; this was a small to medium effect (Deckersbach et al., 2013). This finding contrasts with data from a previous study, which found that comorbid anxiety was a negative moderator of outcomes in a type 1 trial of IPSRT (Frank et al., 2005).

Overall, it is still unclear whether there is a subset of acutely depressed patients with BD for whom psychotherapy would be particularly effective. It is possible that when depression symptoms are particularly severe, or when there is a concrete target for psychotherapy (e.g., anxiety), intensive psychotherapy is indicated for individuals with BD. However, these findings are preliminary and require replication.

TREATMENTS UNDER DEVELOPMENT

Novel psychotherapeutic treatments for BD continue to be developed and tested. These newer treatments aim to ameliorate symptoms associated with the disorder with greater specificity. One such treatment is an adaptation of CBT for insomnia for a BD population; it is called CBTI-BP and involves eight individual psychotherapy sessions that target sleep disturbance. An RCT tested CBTI-BP against a psychoeducational intervention in a group of 58 bipolar patients; the experimental group exhibited greater improvement in sleep and mood symptoms and reduced impairment compared to the control group at the end of treatment and at the 6-month follow-up (Harvey et al., 2013).

Another adaptation of CBT, Mindfulness-Based Cognitive Therapy (MBCT), was originally developed for treatment-refractory unipolar depression (Teasdale et al., 2000). This intervention, which can be delivered in individual or group formats, supplements traditional CBT with training in mindfulness meditation skills. MBCT for BD has been tested in three small type 3 studies, with promising results in terms of feasibility (Weber et al., 2010) and symptom management (Miklowitz et al., 2009a; Deckersbach et al., 2012). An additional study examined individuals with BD within a larger RCT of MBCT for mood disorder patients in remission with a history of suicidal ideation or behavior. Compared to the waitlist control group, subjects with BD (n = 17) in the MBCT group exhibited greater decreases in depressive and anxiety symptoms (Williams et al., 2008).

A number of other open trials provide preliminary data on the feasibility and efficacy of novel psychotherapeutic interventions for BD, including IPSRT monotherapy for unmedicated individuals with bipolar II disorder (Swartz et al., 2009), CBT for the rapid-cycling subtype of BD (Reilly-Harrington et al., 2007), behavioral activation for bipolar depression (Weinstock, Melvin, & Miller, 2013), and a psychoeducation intervention with a focus on regulating responses to goal attainment and reward (Johnson & Fulford, 2009). Continued development and rigorous testing of these innovative psychotherapeutic

interventions may augment the arsenal of effective psychosocial interventions for BD.

INTERNET-BASED APPROACHES

A number of studies have begun to examine the feasibility of use of the Internet as a viable method of delivery of psychoeducation and self-help for BD. One type 1 trial tested a novel Web-based psychoeducation intervention titled "Beating Bipolar." This intervention consisted of eight online modules that provided information on the diagnosis, causes, treatment, and management of BD. The modules featured video-based delivery of information and interactive exercises. Participants were given the opportunity to interact with others, including a study psychiatrist, in an online discussion forum. Fifty participants with BD were randomized to the "Beating Bipolar" intervention or to treatment as usual; the intervention was delivered over a 4-month period. The trial demonstrated positive results in terms of feasibility and participant engagement in the online intervention; however, at the 6-month follow-up, there were no differences between groups on the main outcome measure (overall quality of life) or any of the secondary outcome measures (Smith et al., 2011).

Another type 1 trial examined the efficacy of an eight-session noninteractive, didactic, Web-based audiovisual program that included psychoeducational information about BD as well as personal testimonies and advice from peers and experts. This intervention (n = 139) was compared to an enhanced condition (n = 134), in which participants also received peer support and coaching via e-mail, and a control condition (n = 134), which consisted only of facts about BD delivered via online text. No significant differences were found between groups on mood symptoms or stigmatization (Proudfoot et al., 2012). Thus, while some evidence suggests that online interventions for BD are feasible and engaging, there is no evidence to suggest that these interventions are efficacious, although further studies are under way (Barnes et al., 2011 Todd et al., 2012).

INTERVENTIONS FOR BIPOLAR SPECTRUM CHILDREN AND ADOLESCENTS

There has been growing interest in psychosocial interventions for pediatric-onset BD (see Fristad & MacPherson, 2013, for a more in-depth review). The early-onset form of the disorder is characterized by chronicity of symptoms, rapid cycling, a preponderance of mixed episodes, slow recoveries from acute episodes, and significant psychosocial impairment (Pavuluri, Birmaher, & Naylor, 2005). It may be particularly important to intervene with child- and adolescent-onset BD because the human brain is most malleable at these ages (Giedd, 2004; Spear, 2000). The modification of dysfunctional neurological pathways—via psychosocial interventions, psychopharmacology, or both—may reduce the severity, frequency, and life disruptions of future manic and/or depressive episodes.

Multifamily Psychoeducational Psychotherapy (MF-PEP), a manualized intervention that provides psychoeducation and cognitive and behavioral skills training in a multifamily group format, has been developed and tested for school-aged children with bipolar spectrum disorders. One type 1 study randomized 165 participants (children aged 8 to 11 with mood disorder diagnoses) to eight sessions of MF-PEP or a waitlist control. Children in the MF-PEP group exhibited greater decreases in mania and depression symptoms at the end of treatment and at the 1-year follow-up, and these gains were maintained at the 18-month follow-up (Fristad et al., 2009). Outcome data from two type 2 studies and one open trial (Fristad et al., 2002, 2003) provide additional support for this intervention, including an individual family version (Fristad, 2006) and preliminary data from an implementation trial in a community mental health setting (Macpherson et al., 2013).

FFT has been adapted for bipolar spectrum adolescents (FFT-A); like FFT for adults, the intervention includes psychoeducation sessions about the illness, communication, and problem-solving skills training. FFT-A has been tested in one open trial and one type 1 study. In the type 3 open trial, Miklowitz and colleagues (Miklowitz, Biuckians, & Richards, 2006a) examined a 21-session version of FFT involving 20 bipolar teens (mean age 15 years). All patients received pharmacotherapy and entered FFT following an acute period of illness. Over 2 years, significant improvements were observed in observer-rated depression scores (Cohen's d = 0.87), mania scores (d = 1.19), total mood symptom scores (d = 1.05), and parent-rated Child Behavior Checklist total problem behavior scores (d = 0.99).

In a type 1 RCT of 58 adolescents with BD, participants were randomized to pharmacotherapy plus a three-session psychoeducation intervention, or pharmacotherapy plus FFT-A (Miklowitz et al., 2008). The FFT-A group exhibited faster recovery from baseline depressive symptoms, less time in states of depression, less severe depressive symptoms over time, and more time in remission than patients in the briefer treatment group. One moderator of outcome was high EE: FFT-A was particularly effective in decreasing mood symptoms in adolescents with high-EE families (Miklowitz et al., 2009b).

FFT has also been adapted for children and adolescents at high risk for BD (FFT-HR); these youths have a mood disorder diagnosis (typically major depressive disorder or bipolar not otherwise specified), have exhibited mood symptoms in the past month, and have a first-degree relative with a BD diagnosis. In an open trial of this intervention, 13 families received FFT-HR. High-risk children and adolescents in the trial exhibited improved global functioning and decreased symptoms of depression and hypomania at the 1-year follow-up (Miklowitz et al., 2011).

In a type 1 study of FFT-HR, 40 high-risk children and adolescents were randomized to either FFT-HR or a one- or two-session family psychoeducation control group (Miklowitz et al., 2013). All participants were receiving as-needed pharmacotherapy and had access to crisis intervention sessions during the study. Children and adolescents in the FFT-HR group exhibited faster times to recovery, fewer weeks in symptomatic states, and a more favorable trajectory of hypomanic symptoms than youths in the control condition. High EE was a moderator of treatment outcome (i.e., high-EE families benefitted most from FFT-HR).

Several open trials have provided preliminary data to support the feasibility and efficacy of novel psychotherapeutic treatments for bipolar spectrum children and adolescents. One such intervention is called Child and Family Focused Cognitive Behavior Therapy (CFF-CBT). This family-based 12-session intervention consists of psychoeducation, cognitive-behavioral therapy, and skills training in communication, emotion regulation, and problem solving. In an open trial of CFF-CBT with an individual family format ($n = 34$), bipolar children aged 5 to 17 exhibited reductions in mania, aggression, psychosis, depression, and global functioning scores from pretreatment to posttreatment (Pavuluri et al., 2004); these gains were maintained over a 3-year follow-up (West et al., 2007). Another open trial ($n = 26$, bipolar children aged 6 to 12) tested CFF-CBT in a multiple family format; children exhibited significant improvement in manic symptoms and psychosocial functioning. More rigorous trials of this intervention appear warranted.

Small open trials have also suggested the feasibility of three other psychosocial interventions for bipolar spectrum adolescents: dialectical behavior therapy (with family skills training, individual therapy, and coaching calls as needed; Goldstein et al., 2007), individual CBT with limited family involvement (Feeny et al., 2006), and a version of IPSRT adapted for adolescents (IPSRT-A; Hlastala et al, 2010).

In summary, family interventions are promising adjuncts to pharmacotherapy in stabilizing the course of early-onset BD. The interventions with the strongest empirical support (MF-PEP, FFT-A, and FFT-HR) each include heavy family involvement, as well as psychoeducation and skills training components; these may be the key ingredients necessary for successful psychosocial intervention. Data from two type 1 studies indicate that high-EE families in particular may benefit from this type of intervention. However, precise mechanisms of action (modification of expressed emotion, family interactional behavior, medication adherence, ability to recognize and cope with prodromal symptoms, knowledge of the illness, or social support) and, in turn, whether such improvements map differently onto changes in manic or depressive symptoms remain to be clarified in future trials.

CONCLUSIONS

There are now substantially more randomized trials of psychosocial treatments for BD than in prior editions of this volume. Those studies that have been completed suggest an advantage for patients receiving psychosocial intervention and medication in the domains of time to recurrence, symptom stabilization, and medication compliance. Some evidence also indicates that psychosocial interventions exert positive effects on social, vocational, and global functioning. There remains a pressing need for more controlled research regarding specific psychosocial interventions as adjunctive treatments for this serious disorder. In future studies, it will be important to

compare disorder-specific psychosocial interventions to control conditions that are matched in terms of therapist contact and attention. Of particular importance will be effectiveness studies to examine uptake, feasibility, and outcomes of evidence-based practices in "real-world" (and potentially resource-poor) clinical settings; outcomes from such studies can provide information about which interventions are most amenable to dissemination.

Although they differ in terms of underlying theory, conceptualization, and specific foci, the psychosocial interventions for BD presented here have several components in common. In terms of length of treatment, they ranged from 12 to 30 sessions; the average number of sessions attended across trials was approximately 13 to 15 (Scott & Colom, 2008). Psychoeducation was an important component of each of the interventions, and clinicians worked collaboratively with patients and/or their families to create a shared conceptualization of the illness as it affected the patient. These interventions also shared an emphasis on building skills to manage the illness and helping the patient/family generalize these skills to their daily lives (Miklowitz & Scott, 2009).

Research has begun to shed light on which psychosocial interventions may be most appropriate for various phases of illness in BD. Group psychoeducation has been tested in bipolar patients in remission and is effective in improving medication adherence and preventing manic relapse at both short- and long-term follow-up. Also in remitted patients, caregiver psychoeducation may be useful in delaying recurrence, CBT may be useful in improving dysfunctional negative attitudes and preventing depression, and CR may be useful in improving psychosocial functioning. FFT and IPSRT, on the other hand, have been tested as adjuncts to pharmacotherapy in BD patients who are stabilizing from acute manic or depressive episodes, with promising results. For acutely depressed BD patients on mood stabilizers or atypical antipsychotics, intensive psychotherapies such as FFT, IPSRT, and CBT may be more appropriate treatments for depressive symptoms than adding an antidepressant to the medication regimen. Taken together, these results begin to form a picture of appropriate psychosocial intervention across illness phases for individuals with BD. Replication of these findings, particularly in effectiveness trials, is necessary to continue to hone guidelines for psychosocial intervention.

Despite this growing evidence base, the key components or "active ingredients" necessary for successful psychosocial treatment of BD remain unclear. Potential mediators of treatment outcomes include increased medication adherence, increased self-monitoring and detection of prodromal symptoms, cognitive restructuring, stabilization of sleep/wake cycles, and improved family communication. Future studies with a priori hypotheses regarding potential treatment mediators are necessary. Rigorous identification of mechanisms of change can inform the development of more cost-effective, efficient, and targeted interventions, which are essential to broad-based dissemination.

In addition to further study of potential treatment mediators, continued investigation of treatment moderators is also required. Despite attempts to examine predictors of treatment outcome, it is still unclear whether there are subtypes of patients with BD who benefit the most from specific psychosocial interventions. Moderator analyses from a few studies indicate that psychosocial intervention is more effective for individuals earlier in their course of illness, but evidence for this is mixed. There is some evidence that the efficacy of family interventions is moderated by the family's level of EE or other indicators of family conflict or impairment. The role of comorbid anxiety in the psychosocial treatment of BD is unclear, as conflicting evidence exists regarding its relationship to treatment outcome; this is a topic worthy of further investigation. Overall, consistent patient and family characteristics that predict positive outcomes from various forms of individual, family, or group therapy still need to be identified. Because investigations of mediators and moderators require large sample sizes, meta-analytic methods that combine data from many different trials may be useful in this regard.

Finally, the application of psychosocial interventions during the earliest phases of the disorder (e.g., cases in which the onset has occurred in childhood or adolescence, or in which genetically at-risk children are in subsyndromal, preonset phases) has received more attention since the appearance of previous editions of this volume. Evidence indicates that family psychoeducation and skill building may be important adjuncts to pharmacotherapy in the treatment of bipolar spectrum disorders in children and adolescents. Early intervention may change the long-term trajectory of the illness, which in turn should result in better functional outcomes, lower rates of suicide,

and lower personal and societal costs; however, the long-term impact of early intervention remains to be seen. We do not know, for example, whether early psychosocial intervention reduces the risk of developing BD in high-risk children. Longitudinal follow-up studies of cohorts currently being treated may eventually shed light on this issue.

Thus, next steps include independent replication of efficacious findings, increased specificity in terms of mechanisms of change and moderators of outcome, and implementation considerations such as cost-effectiveness and disseminability. Type 1 clinical trials of specific, manualized treatments, with rigorous control conditions, documentation of treatment integrity, and careful assessment of specific and relevant domains of outcome (e.g., symptoms, social-occupational functioning, medication adherence, sleep/wake cycle regularity, cognitive styles, and family functioning) are essential. The successful investigation of these questions may broaden prevailing views of the treatment of BD beyond purely pharmacological approaches to integrative models that provide more powerful protection against recurrences of the disorder.

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11

Pharmacological Treatments for Unipolar Depression

Stefania Prendes-Alvarez
Alan F. Schatzberg
Charles B. Nemeroff

The treatment of unipolar major depression with antidepressant medication is well established on the basis of scores of randomized placebo-controlled trials involving hundreds of thousands of patients. Tricyclic antidepressants (TCAs) were the first to be studied extensively, and meta-analyses of randomized, placebo-controlled trials show them to be consistently and significantly more efficacious than placebo. Because of a narrow safety margin and a significant drug-induced adverse side effect profile, TCAs have now been replaced as the first-line treatment of depression by selective serotonin reuptake inhibitors (SSRIs: fluoxetine, sertraline, paroxetine, citalopram, and escitalopram), serotonin norepinephrine reuptake inhibitors (SNRIs: venlafaxine, duloxetine, and levomilnacipran), as well as other compounds, including, for example, bupropion and mirtazapine. Each of these agents has been shown to be superior to a placebo and as effective as comparator TCAs or SSRIs in controlled trials. Clinical trials consistently show them to be better tolerated than TCAs, and they clearly have a wider margin of safety. However, controversy continues over whether TCAs are more effective than SSRIs for the treatment of the most severely ill depressed patients. Monoamine oxidase inhibitors (MAOIs), while also more effective than placebo, have generally been reserved for treatment-refractory patients; however, a recently released transdermally delivered selegiline may be used in less refractory patients. It is now generally recognized that patients with recurrent major depression benefit from continued antidepressant treatment, and there is evidence that antidepressants of all classes are effective for the long-term management of recurrent major depression. Additionally, combination and augmentation therapy practices are gaining in popularity for patients who are partial responders and nonresponders to monotherapy. An important issue in evaluating the antidepressant literature is to distinguish between response rated as a reduction in the level of symptoms on a rating scale and response rated as true remission from illness.

INTRODUCTION

Major depressive disorder is a chronic syndrome associated with high mortality (secondary to suicide and increased rates for heart disease, stroke, and other serious diseases), and it is one of the most common medical disorders affecting adults in the world today. In the United States, the lifetime prevalence of major depression is 16.7% for adults (Kessler et al., 2005). The average age of onset is 32 years, and women are 70% more likely to develop depression than men (Kessler et al., 2003). Neither the core requisite

symptoms for the diagnosis of a major depressive episode nor the required duration of at least 2 weeks has changed from the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) to *DSM-5*.

In this chapter we discuss the main issues surrounding the treatment of major depressive disorder, such as suicidality and goals of treatment, as well as provide the most up-to-date information about all treatment options approved by the U.S. Food & Drug Administration (FDA). Drugs are categorized by their known mechanisms of action and discussed as such.

The efficacy of antidepressant medications has been well established in a myriad of controlled clinical trials, and in general the response of patients with unipolar depression is comparable to the success rates of treatment of major medical disorders such as coronary artery disease (by angioplasty), hypertension, and diabetes. Antidepressants are actually one of the most commonly prescribed classes of medications in the United States. Meta-analyses of the vast database of double-blind, placebo-controlled clinical trials have revealed a highly statistically significant effect of all of the currently available antidepressants approved by the FDA for the management of acute unipolar depression. No other mental illness has received this much scrutiny. Because the FDA approval process usually involves comparison to both a placebo and an already approved antidepressant, such as a TCA, large numbers of patients, literally thousands, have been involved in these trials. While some meta-analyses suggest that the efficacy of antidepressants for major depression is overstated and limited to severe depression, a recent reanalysis of trials concluded that antidepressants are indeed efficacious and baseline severity is not significantly related to degree of treatment advantage over placebo (Gibbons et al., 2012).

The monoamine hypothesis of depression states that monoamines, such as serotonin, norepinephrine (NE), and dopamine (DA), may be relatively deficient in the central nervous system (CNS) of depressed patients. Although this hypothesis has not proven accurate in describing the pathophysiology of depression, the majority of the antidepressants currently available in the United States act in one way or another to increase these monoamine levels in the brain, and they are usually classified by their purported neurochemical mechanism of action (Table 11.1). Not only have all of the listed antidepressants been demonstrated to be effective in treating major depression, but no single antidepressant has ever been conclusively demonstrated to be more effective than any other antidepressant (Nemeroff, 1994). A recent study investigated this further and found that observed mood and cognitive symptoms improved more with escitalopram, an SSRI, than with nortriptyline, a TCA. However, neurovegetative symptoms improved more with nortriptyline than with escitalopram (Uher et al., 2009). Thus, physicians must consider the clinical presentation of their patients when deciding which medication to prescribe. There is also some controversy (see below) regarding whether antidepressants that interact with more than one monoamine receptor system, such as venlafaxine, duloxetine, mirtazapine, and TCAs, might be more effective than the others, particularly for severe or treatment-refractory depression.

TABLE 11.1 Tricyclic and Tetracyclic Agents: Pharmacological Effects

	Reuptake Blockade		*Receptor Blockade*		
Drug	*NE*	*5-HT*	*ACh*	H_1	α_1
Imipramine	+	+	++	+	++
Desipramine	+++	0	+	0	+
Amitriptyline	±	++	++++	++++	+++
Nortriptyline	++	±	++	+	+
Doxepin	++	+	++	+++	++
Trimipramine	+	0	++	+++	++
Protriptyline	++	0	+++	+	+
Clomipramine	+	+++	++	+	++
Maprotiline	++	0	+	++	+
Amoxapine	++	0	0	±	++

Note: Based on Potter, Manji, and Rudorfer (1998). Reprinted with permission.

NE = norepinephrine; 5HT = serotonin; ACh = acetylcholine; H_1 = histamine-1; α_1 = alpha-1; + = mild effect; ++++ = marked effect.

One important issue to discuss in this chapter is, of course, the definition of response in an antidepressant drug trial. A 50% decline in a dimensional measure of depression severity, such as the Hamilton Depression Rating Scale (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS), is the generally accepted definition of a responder. However, many patients with severe depression (HAM-D scores, for example, greater than 28) can exhibit a 50%

improvement in depression severity and therefore are defined as responders but have considerable residual depressive symptoms (e.g., a HAM-D score of 13). Thus, patients included as responders may, in fact, be partial responders and clearly not euthymic. More stringent definitions of response (i.e., remission) include HAM-D scores of less than 7 or some other measure of euthymia. Additionally, while response was once the goal of depression treatment, this has shifted in recent years to remission and recovery without relapse and recurrence. Remission is defined as the removal of essentially all symptoms; recovery is when this is sustained for longer than 6 months (Stahl, 2013). If depression returns before or during remission, it is called relapse; if it returns after a patient has recovered, it is termed recurrence (Stahl, 2013). These are critical concepts to understand when reviewing the literature on treatments for unipolar depression, and we must understand that leaving patients with residual symptoms predisposes them to a full relapse of depression within a much shorter time than if remission were achieved. A brief questionnaire was distributed to 535 patients being treated for major depressive disorder and they were asked to rate the importance of 16 statements in determining whether their depression was in remission. The three items that were most frequently judged to be important were (1) the presence of features of positive mental health (optimism, self-confidence); (2) return to one's usual, normal self; and (3) return to usual level of functioning (Zimmerman et al., 2006). Indeed, there is increasing awareness that symptom severity and functional outcomes in the treatment of major psychiatric disorders are often not tightly correlated (Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006), suggesting the importance of real-world function in assessing recovery.

A somewhat poorly understood issue regarding the treatment of unipolar depression is the response of depressed patients to placebo, which can occur at surprisingly high rates in clinical trials comparing a placebo and an antidepressant. This is no trivial issue because, as previously mentioned, novel antidepressants must be shown to be statistically superior to placebo and usually as efficacious as an already approved antidepressant in order to receive FDA approval. This subject has previously been discussed in considerable detail (Schatzberg & Kraemer, 2000), but the primary point to be made to the reader who is not familiar with clinical psychopharmacology trials in depression is that placebo treatment is *not* identical to no treatment. Patients enrolled in clinical trials spend considerable periods of time with the staff (research nurses, research assistants) as well as with the trial physicians. This is equally true for patients in the intervention and the placebo arm. The quantity of time spent by patients in clinical trials (often several hours each week) far exceeds the time spent by a patient treated by a mental health professional in a "standard" fee-for-service setting or managed-care setting. This contact between the patient and the research team clearly has effects on the patient's clinical state. Alternative approaches to evaluating the meaningfulness of clinical effects have been reviewed in detail elsewhere (Kraemer & Kupfer, 2006; Schatzberg & Kraemer, 2000). Another suggested explanation of this placebo response phenomenon is the idea that some subjects in clinical trials may really be "symptomatic volunteers" who are less ill and less complicated than "real" patients (Stahl, 2013). Perhaps this explains why a recent meta-analysis concluded that the magnitude of benefit of antidepressant medication compared with placebo increases with severity of depression symptoms, and for patients with very severe depression the benefit of medications over placebo is substantial (Fournier et al., 2010).

Another issue that has received considerable attention is the rapidity of response to antidepressants. It is generally acknowledged that antidepressants require 3 to 5 weeks before their therapeutic response is clinically evident, likely due to their effects on receptor regulation and/or gene expression. Specifically, the amount of neurotransmitter available in the synaptic cleft changes relatively rapidly when an antidepressant is administered, but both the clinical effects and changes in receptor sensitivity are delayed. This temporal correlation of clinical effects with changes in receptor sensitivity has given rise to the neurotransmitter receptor hypothesis, which states that depression is caused by upregulation of certain receptors and thus antidepressant efficacy is related to downregulation of receptors (Stahl, 2013). This downregulation occurs as a result of the increased extracellular concentrations of neurotransmitters in the CNS that is the primary mechanism of action of many antidepressant drugs. There is also evidence that the delay in therapeutic effects of antidepressants may be secondary to changes in gene transcription.

This is a very complex issue, and space constraints preclude a comprehensive discussion of this

controversial topic. Another hypothesized mechanism underlying antidepressant response is increased neurogenesis in the hippocampus, an effect that parallels the time course of clinical response. However, it is important to note that the so-called lag time in antidepressant drug response in clinical trials is, of course, a mean of patients who respond relatively quickly, patients who respond after a few weeks, and patients who are nonresponders. In addition, the definition of response, as described above, obviously has a major impact here; few patients show complete euthymia after 1 week. It used to be thought that if patients do not respond to antidepressants after 4 to 6 weeks, they should be treated for an additional 4 to 6 weeks. However, several studies (Boyer & Feighner, 1994; Nierenberg et al., 1995) have revealed that if the patient has not responded to paroxetine by 3 weeks of treatment or fluoxetine by 4 weeks of treatment, there is little likelihood that additional treatment, at that dose, will be successful. Dose escalation has also not proven to be effective, and this is discussed in greater detail below. Pipamperone, an antipsychotic drug, administered at low doses, acting primarily as a $5HT_2$ receptor antagonist, in combination with citalopram was reported to accelerate the antidepressant effects compared with citalopram plus placebo (Wade et al., 2011), but a second study did not confirm these findings.

Unfortunately, a generation of studies attempting to identify biological markers that predict treatment response to one or another antidepressant failed to provide valid predictors of either response or nonresponse to any antidepressant drug class. However, pharmacogenetics and brain imaging offer considerable potential for predicting response (Murphy, Kremer, Rodrigues, & Schatzberg, 2003a, 2003b; Murphy, Hollander, Rodrigues, Kremer, & Schatzberg, 2004). For example, the short form of the serotonin transporter promoter may predict poor response to an SSRI or intolerance to such therapy (Murphy et al., 2004). Functionally, the use of positron emission tomography (PET) to label neurotransmitter transporters and receptors in vivo may provide for the first time the ability to determine whether a given patient shows, for example, a deficit in serotonin transporter binding, which might predict response to SSRIs.

Other critical areas that the reader might wish to consider are issues of age, gender, and comorbid medical disorders. For many years, there was a widespread belief among clinicians that antidepressants are effective for children and adolescents, but few controlled studies had demonstrated such efficacy (see DeVane & Sallee, 1996, and Fisher & Fisher, 1996, for a review). Now, evidence for the efficacy of fluoxetine (Emslie et al., 1997), paroxetine (Keller et al., 2001), and citalopram (Wagner et al., 2004) in children and adolescents is available. There are many failed reports of efficacy of various classes of antidepressants in the elderly (Roose & Schatzberg, 2005; Schatzberg & Roose, 2006). This group tends to manifest high placebo response rates, although here too there are several positive trials with second-generation agents. The exclusion of women of childbearing potential from clinical trials because of fears of potential teratogenic effects of antidepressants has resulted in an embarrassing lack of knowledge of pharmacokinetics and clinical efficacy in the population that has the highest prevalence rate of unipolar depression. Further studies with a focus on antidepressant–gonadal–steroid interactions are advisable.

Of paramount importance is the documentation of antidepressant efficacy and tolerability in patients with comorbid medical disorders. Prevalence rates of unipolar depression in patients with medical disorders such as cancer, diabetes, myocardial infarction, cardiovascular disease (CVD), Parkinson's disease, multiple sclerosis, stroke, and Alzheimer's disease are remarkably high (25% to 50%), and for many years relatively few controlled treatment trials had been conducted in these populations (see Boswell, Anfinson, & Nemeroff, 1997, for a review). Depression in patients with CVD is associated with an increased risk of morbidity and mortality, and treatment of depression has been hypothesized to reduce cardiac mortality. A recent search of the PubMed and PsychINFO databases provided considerable evidence from randomized controlled clinical trials that SSRIs are safe in the treatment of major depression in patients with CVD (Mavrides & Nemeroff, 2013). Additionally, a recent systematic review and meta-analysis of randomized controlled efficacy trials of antidepressants in patients with depression and chronic medical disorders demonstrated that SSRIs and TCAs are efficacious and safe (Taylor et al., 2011). In this study, SSRIs were shown to improve quality of life over TCAs, an important finding to consider when deciding what to prescribe. Additional studies in this area are vitally important to conduct because of the increasing evidence that depression is associated with an increased risk of morbidity and death following events such as a myocardial infarction or stroke.

Since the majority of patients with medical disorders are prescribed a variety of other medications, it is also of paramount importance to prescribe antidepressant medications that are safe and, in particular, have no drug–drug interactions with other prescribed medications. This is not a trivial issue because most antidepressants are bound to plasma proteins and therefore can displace other commonly prescribed drugs, such as coumadin, from their protein-binding sites. In a case like coumadin, this would result in increasing plasma drug concentration, thereby increasing bleeding times, with potentially adverse consequences. Moreover, some antidepressants inhibit the activity of certain hepatic cytochrome P_{450} isoenzymes, which are responsible for metabolizing a wide variety of other commonly prescribed medications. Such drug–drug interactions, if not acknowledged, could lead to increases in plasma concentrations of drugs. These data have been comprehensively reviewed (DeVane, 1994; Ereshefsky, 1996; Nemeroff, DeVane, & Pollack, 1996). Of note, however, is that for nontricyclic agents, slow drug metabolism seems to be a less pressing and potentially less dangerous issue (Murphy et al., 2003b).

Yet another area of crucial importance is maintenance/continuation treatment of depression and assessment of its efficacy compared with placebo treatment. This is particularly important considering the shift in treatment goal from response to remission and recovery. For many years, it was generally recommended that, after a single episode of depression, patients should be treated for 6 months. If a patient has suffered more than one episode of depression, if the first episode was particularly severe (e.g., with a serious suicide attempt) or particularly difficult to treat, or if the patient has a very strong family history, long-term treatment should be considered. All of the reported studies that have evaluated treatment with antidepressants for 1 year or longer compared with a placebo have found highly significant beneficial effects of antidepressant treatment. Such studies have included TCAs, SSRIs, venlafaxine, and so forth. For instance, in patients with type 2 diabetes mellitus who had recovered from major depression, maintenance therapy with sertraline prolongs the depression-free interval (57 days to 226 days) (Lustman et al., 2006). Sustained remission needs to be the goal for these patients because it is also associated with improvements in HgA1c levels (Lustman et al., 2006) Data on maintenance therapy have been reviewed extensively (Blacker, 1996; Hirschfeld & Schatzberg, 1994; Kornstein et al., 2006; Perahia et al., 2009; Thase & Sullivan, 1995). One seminal study in this area is the PREVENT Study (Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years). Patients with recurrent unipolar depression were initially randomized to venlafaxine extended-release (ER) or fluoxetine for 10 weeks of acute treatment. Responders then received 6 months of continuation treatment with the drug they were initially randomized to receive. Continued responders were subsequently enrolled in two 12-month maintenance periods. Results showed that those who were successfully treated with venlafaxine ER during the acute and continuation phases were significantly less likely to experience recurrence with continued venlafaxine ER than with placebo in both maintenance phases (Keller et al., 2007; Kocsis et al., 2007). These data point toward the need to view unipolar depression as a chronic condition that benefits from long-term treatment. More about maintenance treatment will be discussed below for different classes of antidepressants.

A point should be made about the use of more than one medication to treat depression. For many years, the prevailing opinion in psychiatry had been that monotherapy for depression is highly desirable and, conversely, that polypharmacy is to be avoided. This is certainly not the case in other branches of medicine, in which treatment with two or three drugs is virtually the rule. Failure of a single agent to provide adequate control of hypertension, diabetes, or a neoplasm invariably leads to the use of two or three pharmacological agents. If the goal is to return the patient to complete euthymia, combination therapy with more than one psychotropic agent, as well as combination psychopharmacology and psychotherapy, may be necessary. Indeed, some combinations—for example, addition of antipsychotics—may rapidly convert nonresponders to responders (Shelton et al., 2001). Blier and colleagues recently reported that combination therapy from treatment initiation with mirtazapine plus fluoxetine, mirtazapine plus venlafaxine, and mirtazapine plus bupropion is just as well tolerated and more clinically effective than fluoxetine alone (Blier et al., 2009). In contrast, however, Rush and colleagues compared two antidepressant medication combinations with SSRI monotherapy, and neither combination outperformed monotherapy (Rush et al., 2011). Please refer to the chapter section titled

"Combination and Augmentation Therapy" for further information.

More than 35,000 individuals die in the United States by suicide every year. In 2003, an FDA advisory warned that antidepressants may be associated with an increased risk of suicidal thoughts and behaviors in adolescents, and in 2006 they recommended that the black box warning be extended to include young adults. This has brought about much attention to the topic and has recently been reviewed (Ryan & Nemeroff, 2014). Meta-analyses of trials in adults have found no overall increase in risk. Instead, increases in prescriptions for SSRIs and new-generation non-SSRIs are associated with lower suicide rates (Gibbons, Hur, Bhaumik, & Mann, 2005). This may reflect the efficacy of these antidepressants, increased adherence, and a better quality of mental health care. Additionally, a reanalysis of the randomized, placebo-controlled studies of fluoxetine and venlafaxine showed that these two drugs actually decreased suicidal thoughts and behavior for adult and geriatric patients (Gibbons, Brown, Hur, Davis, & Mann, 2012). This protective effect is most likely mediated by decreases in depressive symptoms with treatment. It must be noted, though, that while current antidepressant use has not been associated with completed suicide and death, it has been associated with an increased risk of attempted suicide (Tiihonen et al., 2006). The low therapeutic index and risk of fatality after overdose of some antidepressants is discussed below.

Before discussing the different antidepressant classes below, we will summarize the results from the largest and longest effectiveness study ever conducted to evaluate depression treatment—the STAR*D (Sequenced Treatment Alternatives to Relieve Depression). The treatments used in the study include citalopram, sertraline, bupropion, venlafaxine, mirtazapine, nortriptyline, tranylcypromine, lithium, thyroid hormone (triiodothyronine, T3), buspirone, and cognitive-behavioral therapy (CBT). The study design consisted of four levels, each with a different treatment or medication combination. The primary goal of each level was to determine whether the treatment used could optimally treat the patient's depression—and if not, whether the next levels could treat it. Important to keep in mind is that the STAR*D outcome measure was remission. In level 1, approximately one third of participants reached remission in an average of 7 weeks. About 25% of participants became symptom-free in the level 2 switch group, 12% to 20% in level 3, and 7% to 10% in level 4. Overall, these results show that patients with depression who are difficult to treat can indeed get well after trying several treatment strategies, but the odds of remission decrease with every additional treatment strategy needed (Fava et al., 2006; McGrath et al., 2006; Rush et al., 2006).

TRICYCLIC ANTIDEPRESSANTS

TCAs were for many years the mainstay of treatment for major depression. They are so named because of their chemical three-ringed structure. They were introduced into the United States in the 1960s after the discovery that they had antidepressant properties when they failed as antipsychotic drugs. In this country, seven TCAs are approved for treatment of major depression, and one additional compound—clomipramine—is approved for obsessive-compulsive disorder (OCD) but is viewed throughout the world as an efficacious antidepressant as well. Two other compounds (maprotiline and amoxapine) have four-ringed structures and are variants of the tricyclic class.

The TCAs as a class are potent inhibitors of the reuptake of NE into presynaptic neurons; they exert fewer effects on serotonin reuptake, although this is dose-dependent (see Table 11.1). The one major exception is clomipramine, which is a potent serotonin reuptake blocker with a demethylated metabolite that is a potent NE reuptake blocker. Additionally, some TCAs are antagonists at serotonin receptors ($5HT_{2A}$ and $5HT_{2C}$) (Stahl, 2013). NE reuptake blocking effects probably account for some patients' becoming activated (increased anxiety or agitation) on these agents. Generally, such effects are dose-related and can be minimized by conservative dosing and gradual dose increases. TCAs are documented antianxiety agents after chronic dosing.

There is vast literature demonstrating efficacy of the TCAs (Potter, Manji, & Rudorfer, 1998). In the United States, some of the original randomized clinical trials (RCTs) in psychiatry included imipramine or amitriptyline and showed these agents to be effective in what we now term *major depression*. Efficacy of the TCAs has been revisited in SSRI comparator trials, and the TCAs still appear to be more effective than a placebo and to be of comparable efficacy to the

SSRIs. However, SSRIs have an advantage over TCAs in terms of tolerability. Janicak, Davis, Preskorn, and Ayd (1993) performed meta-analyses of the TCA RCT literature and reported these antidepressants to be overwhelmingly more effective than a placebo. For example, 50 studies that had compared imipramine with a placebo reported an aggregate response rate to the TCA of 68%, compared with a 40% response rate to the placebo, a difference significant at the $p < 10^{-40}$ level. Intention-to-treat response rates for placebo-controlled studies of imipramine in outpatients were 51% for imipramine and 30% for placebo (Nelson, 2013).

The efficacy of TCAs appears to vary in different subtypes of depression. Some investigators have argued that the TCAs are more effective than SSRIs in the treatment of more severely depressed or melancholic inpatients in that they are more likely to induce remission within 4 to 6 weeks. In a study by the Danish University Antidepressant Group (1990), clomipramine produced significantly higher rates of remission than did paroxetine (an SSRI). In another report on inpatients by this group (Danish University Antidepressant Group, 1986), clomipramine was also significantly more effective than citalopram (another SSRI). Roose, Glassman, Attia, and Woodring (1994) reported that nortriptyline was more effective than fluoxetine (yet another SSRI) in hospitalized cardiac patients with melancholia. Other studies have found that TCAs and SSRIs have comparable efficacy, although the perception of superior efficacy persists among some investigators.

Monotherapy with TCAs is less effective in major depression with psychotic features (delusional depression) or in those with so-called atypical features. In the former, TCA monotherapy has been found to be effective in only 35% of patients, in contrast to a 65% response rate in their nondelusional counterparts, a difference that is highly statistically significant (Chan et al., 1987). In delusional depressives, TCAs in combination with antipsychotics have been reported to be significantly more effective than TCAs alone (Schatzberg & Rothschild, 1992). For such patients, clinical practice now calls for combining TCAs or other antidepressants with antipsychotic agents. The presence of atypical features (hypersomnia, hyperphagia, prominent anxiety, reverse diurnal mood variation) predicts poorer responses to imipramine than to MAOIs according to some RCTs (see below).

The TCAs all have some affinity for muscarinic cholinergic receptors as antagonists (see Table 11.1) and therefore can cause dry mouth, blurred vision, constipation, urinary hesitancy, memory disturbance, and tachycardia. Agents within the class vary in the degree to which they produce these side effects, with the so-called secondary tricyclics, which represent demethylated metabolites of parent tertiary TCAs, exerting less anticholinergic effects than their parents. Examples are nortriptyline (the metabolite of amitriptyline) and desipramine (the metabolite of imipramine). The TCAs are also antihistaminic, with amitriptyline and doxepin being most potent at this site (see Table 11.1) and being most likely to produce sedation and weight gain. These agents also block α_1-adrenergic receptors and produce orthostatic hypotension. Here, too, these side effects are mainly dose-related and can be minimized by using lower doses of drugs, particularly when initiating treatment. Some patients may, however, not be able to tolerate even the most minimal doses of these agents.

Because of their α_1-adrenergic and anticholinergic effects, and because they weakly block voltage-sensitive sodium channels in the heart and brain, the TCAs are potentially cardiotoxic in overdose and have relatively narrow safety margins (low therapeutic index).

Generally, clinicians initiating treatment with a TCA begin at low doses (e.g., 50 mg of amitriptyline, imipramine, or desipramine or 25 mg of nortriptyline) to avoid side effects as much as possible and to maximize adherence. Over 7 to 10 days, doses are increased gradually to 150 mg/day of amitriptyline, imipramine, or desipramine or to 75 mg/day of nortriptyline. After 2 weeks of these doses, further gradual dosage increments can be undertaken to achieve the maximum recommended doses. Therapeutic dosage ranges are summarized in Table 11.2. Plasma concentrations of the TCAs can also help guide optimal dosing; this is especially important with the TCA nortriptyline.

Maintenance therapy with the TCAs has been the focus of two major studies. In one, Prien and colleagues (1984) reported relatively low efficacy for maintenance imipramine therapy; however, in that study patients were often maintained at relatively low doses, which reflected the common practice of the day. In another study by Frank and colleagues (1990), imipramine was clearly demonstrated to be more effective than placebo in 3-year maintenance

TABLE 11.2 Typical Therapeutic Dosage Ranges of Tricyclic and Tetracyclic Antidepressant Drugs (Adult Patients)

Drug		
Generic Name	*Trade Name*[*]	*Therapeutic Dose Range (mg/day)*
Imipramine	Tofranil	150–300
Desipramine	Norpramin	150–300
Amitriptyline	Elavil	150–300
Nortriptyline	Pamelor, Aventyl	50–150
Doxepin	Sinequan	150–300
Trimipramine	Surmontil	150–200
Clomipramine	Anafranil	75–200
Maprotiline	Ludiomil	75–200
Amoxapine	Asendin	200–400
Protriptyline	Vivactil	5–60

[*]Original trade names—all are now generic.

therapy of recurrent unipolar depression (20% recurrence on imipramine vs. approximately 90% on the placebo). This study maintained patients at the doses to which they had responded. Moreover, lower-dose versus full-dose maintenance strategies were tested in a subset of subjects (Frank et al., 1993), and full doses were significantly more effective than half doses (30% vs. 70% recurrence, respectively). Thus, maintenance therapy with TCAs appears to require continuing patients on the doses effective during acute treatment, and this should be standard practice.

In conclusion, the TCAs are extremely effective for the treatment of depression, but their multiple actions lead to undesirable adverse effects that make it unlikely that there will be a resurgence of interest in this class, except in patients who have failed to respond to other antidepressants.

MONOAMINE OXIDASE INHIBITORS

The development of the MAOIs is one of the most interesting chapters in the history of psychopharmacology. When tuberculosis was ravaging civilizations and patients infected with the tubercular bacillus were admitted to sanitariums for long-term care, new antitubercular drugs were tested for efficacy in these settings. One such antitubercular drug, iproniazid, was noted to produce mood elevation in many patients. This led to the development of the three MAOIs still approved for depression in the United States: phenelzine, tranylcypromine, and isocarboxazid. These are all irreversible (enzyme activity returns only after new enzyme is synthesized about 2 to 3 weeks after the drug has been discontinued), nonselective (i.e., inhibit both A and B isoforms) MAOIs and, compared with newer antidepressants (see below), have a less favorable side-effect profile.

The MAOIs are believed to produce their therapeutic effects by preventing the degradation of monoamines, particularly serotonin (5-HT), NE, and DA. The enzyme monoamine oxidase exists in two forms, A and B. MAO A metabolizes NE, 5-HT, and DA in the brain and important aminergic compounds (e.g., tyramine) in the gut. MAO A inhibition in the gut necessitates patients being placed on dietary restrictions (see below). MAO B metabolizes DA, tyramine, and phenylethylamine. Inhibition of MAO B alone is not an effective antidepressant action; inhibition of MAO A activity in the brain appears to be key for achieving antidepressant response.

All of the available MAOIs have been shown to be effective in the treatment of unipolar depression and, in particular, atypical depression characterized by hypersomnia and hyperphagia (Krishnan, 2004). Table 11.3 lists the currently available MAOIs and their usual dose ranges. In addition to unipolar depression, MAOIs also appear effective, like SSRIs and certain TCAs, in the treatment of panic disorder. They are also effective in the treatment of bipolar depression. One disadvantage of oral MAOIs include the necessity of dosing multiple times per day, which is associated with considerably poorer compliance

TABLE 11.3 Monoamine Oxidase Inhibitors

Drug		
Generic Name	*Trade Name*	*Dose Range (mg/day)*
Phenelzine	Nardil	45–90
Tranylcypromine	Parnate	10–30
Isocarboxizid	Marplan	10–30
Selegiline[*]	Emsam[*]	6–12[*]

[*]Transdermal delivery.

when compared with once-a-day dosing. Additionally, misinformation about diet and drug interactions acts as a barrier to using MAOIs, so it is prudent to address these two issues in this chapter.

Tyramine, in the presence of MAO A and B inhibition, accumulates and displaces NE from vesicles, and this increased availability of NE can elevate blood pressure. For this reason, patients taking MAOIs are advised to follow a diet low in tyramine. There is a common myth, though, that patients taking MAOIs must avoid all cheeses, as well as beer and wine. In reality, only aged cheeses and tap and nonpasteurized beers need to be avoided. With regard to wine, many wines are actually quite low in tyramine. A patient who ingests more tyramine than suggested can subsequently experience a hypertensive crisis, also known as the "cheese reaction," which is characterized by severe hypertension and possible medical sequelae including stroke. Symptoms of this syndrome include severe headache, flushing, palpitations, and nausea. For a complete discussion of food restrictions necessary for patients taking an MAOI, the reader is referred to the National Institutes of Health Clinical Center Drug-Nutrient Interaction Task Force (http://www.cc.nih.gov/ccc/patient_education/drug_nutrient/maoi1.pdf)

Recently, a transdermal formulation of selegiline has been approved in the United States for treating major depression. At low doses, oral selegiline is an MAO B inhibitor, and at these doses, it does not require dietary restrictions. We have already noted, though, that isolated MAO B inhibition does not have antidepressant properties. When delivered transdermally, selegiline appears to exert MAO A and B inhibition in the brain but does not inhibit MAO A in gut. This obviates the need for dietary restrictions, particularly at the lowest dose (i.e., 6 mg/day). A double-blind, placebo-controlled, dose-titration trial of the selegiline transdermal system (STS) for the treatment of major depressive disorder provided evidence of short-term efficacy, safety, and tolerability in the dose range of 12 mg/day (Feiger et al., 2006). In another study, patients receiving STS had significantly fewer relapses, and when they did relapse, the time to relapse was significantly longer compared with placebo (Amsterdam & Bodkin, 2006). At doses greater than 12 mg/day it is possible that a patient could experience a hypertensive reaction if tyramine is ingested or a sympathomimetic amine is taken, and therefore diet and drug restrictions that apply to nonselective MAOIs should be imposed. There is also the possibility of local skin reactions at the site of selegiline patch placement.

There are two general types of dangerous drug interaction with MAOIs: (1) sympathomimetics that can raise blood pressure and (2) medications that inhibit serotonin reuptake and can cause a potentially fatal serotonin syndrome. In the first category, patients should avoid taking decongestants, stimulants, and antidepressants with NE reuptake inhibition, many of which are available without prescription. General and local anesthetics that contain epinephrine should also be avoided because they can cause changes in blood pressure. In the second category, physicians should avoid prescribing antidepressants (SSRIs, SNRIs, and clomipramine) and certain opiates (e.g., meperidine, tramadol, methadone, and fentanyl). One must also obtain a thorough history of substance use from the patient because some drugs of abuse (e.g., Ecstasy, cocaine, methamphetamine) can adversely interact with MAOIs.

In addition to the drug–drug and drug–food interactions noted above, MAOIs have a number of other untoward side effects, including orthostatic hypotension, sexual dysfunction, weight gain, dizziness, insomnia, tachycardia, palpitations, and edema.

Lastly, the issues of switching patients to and from MAOIs should be addressed. When trying to switch a patient on a serotonin reuptake inhibitor to an MAOI, one must wait at least five half-lives after discontinuing the serotonergic drug before starting the MAOI. If trying to switch in the other direction, one must wait at least 14 days after discontinuing the MAOI. These recommendations should be followed to avoid the risk of serotonin syndrome. Switching between MAOIs also requires a waiting period.

The MAOIs have not been generally considered first-line treatments for depression because of their unfavorable side-effect profile, dietary restrictions, need for dosing multiple times per day, and the general unavailability of platelet MAO activity measurements. They did appear to be more effective than the TCAs and perhaps the SSRIs for patients with so-called atypical depression characterized by leaden limb paralysis, lack of reactivity, hypersomnia, and so forth. Although reversible MAOIs with a more favorable side-effect profile have been developed (e.g., moclobemide), they are not available for clinical use in the United States.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Since their introduction in 1988, the SSRIs have become first-line treatments (Rush & the Depression Guideline Panel of the Agency for Health Care Policy and Research, 1994) for most patients with major depression (Table 11.4). The first of these agents was fluoxetine, and since then five others have been released in the U.S. market: sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. Of these, fluvoxamine is approved for use in the United States only for OCD, although it is used as an antidepressant in many other countries. In this chapter, we focus on the SSRIs approved for major depression in the United States. All of these have the same mechanism of action: They inhibit the reuptake of serotonin (also known as inhibition of the serotonin transporter). They have virtually no effect to date on blocking NE reuptake (except paroxetine at high doses), and they also do not interfere with various ligands binding to muscarinic cholinergic, α_1-adrenergic, or histamine H_1 receptors. Thus, they produce little if any dry mouth, constipation, or urinary hesitancy (anticholinergic effects), orthostatic hypotension (α_1-adrenergic blockade), or sedation and weight gain (H_1 blockade).

The efficacy of the SSRIs has been clearly demonstrated in numerous RCTs, and these data have been reviewed elsewhere (Nemeroff, 1994). Published data are most extensive for fluoxetine, sertraline, and paroxetine, with these drugs having been studied in several thousand patients. In the RCTs published before the release of fluoxetine that formed the basis of the FDA submission, fluoxetine was significantly more effective than placebo in four placebo-controlled studies and was generally comparable to TCAs in six comparison trials (Schatzberg, 1995a). Additionally, significantly fewer patients on fluoxetine discontinued treatment because of adverse events (Bech et al., 2000). Fluoxetine was also reported in the early trials to be "activating," likely because of its $5HT_{2C}$ antagonist properties. Some clinicians and investigators therefore advised against using it in depressed patients with prominent anxiety. Analyses of the comparative clinical trials have subsequently revealed that the drug is as effective in anxious depressives as it is in major depressives without anxiety (Schatzberg, 1995b; Tollefson, Holman, & Sayler, 1994). Some patients may, however, require starting at a lower dose (e.g., 10 mg/day of fluoxetine). The potential "activating" property has also led some to believe that it should be strongly considered for patients with reduced positive affect, hypersomnia, psychomotor retardation, and fatigue. Significant SSRI efficacy in purely anxious patients (e.g., panic disorder) has been revealed in RCTs as well. Thus, the SSRIs (including fluoxetine) appear effective in both depressed and anxious patients or in those who demonstrate mixed symptoms. Subsequent to the FDA submission, thousands of papers have appeared in the archival literature that continue to show significantly greater efficacy for fluoxetine over placebo in patients of all age groups with major depression. Two RCTs of fluoxetine in children and adolescents with major depression have found the drug to be significantly more effective than placebo in that age group as well (Emslie et al., 1997). Additionally, fluoxetine is the only SSRI approved for the treatment of bulimia.

There has been an ongoing debate regarding whether the SSRIs, particularly fluoxetine, are as effective as the TCAs and more recently the dual uptake blockers (discussed below) in the treatment of patients with severe depression. These data have been reviewed in detail elsewhere (Anderson, 1998; Schatzberg, 1996; Thase, Entsuah, & Rudolph, 2001). Although there are occasional reports in the literature that an SSRI was less effective in these subjects, the overall data from RCTs does not bear out this conclusion. In one study, we compared desipramine and fluoxetine in a group of moderately to severely depressed patients (Bowden et al., 1993). The two drugs were of comparable efficacy, but fluoxetine had

TABLE 11.4 Typical Antidepressant Therapeutic Dosage Ranges of Selective Serotonin Reuptake Inhibitors (Adult Patients)

Drug		
Generic Name	*Trade Name*	*Therapeutic Dose Range (mg/day)*
Fluoxetine	Prozac	20–80
Paroxetine	Paxil	20–50
Paroxetine	Paxil CR	25–75
Sertraline	Zoloft	50–200
Citalopram	Celexa	20–40
Fluvoxamine	Fluvoxamine	100–300
Escitalopram	Lexapro	10–20

a far more benign side-effect profile. In a small-scale study of more severely depressed inpatients, Clerc, Ruimy, and Verdeau-Palles (1994) reported that venlafaxine (a dual 5-HT/NE uptake blocker) was significantly more effective at 4 to 6 weeks than fluoxetine. Subsequently, Thase, Entsuah, and Rudolph (2001) reported on a pooled analysis of eight studies comparing venlafaxine with SSRIs and reported a significantly greater response with venlafaxine. Further analyses that included a larger pool of studies pointed to the superiority of venlafaxine over fluoxetine but not over other SSRIs, particularly paroxetine (Nemeroff et al., 2003). Most recently, though, the GENPOD RCT tested the hypothesis that individuals with more severe depression would benefit more from noradrenaline reuptake inhibitors than SSRIs, but this did not end up being the case (Wiles et al., 2012). Thus, the debate is likely to continue for some time, although to date the data overall do not support the impression of lesser efficacy of SSRIs compared to SNRIs for severe depression.

All SSRIs have been reported to be significantly more effective than placebo in preventing relapse or recurrence for up to 1 year of treatment. For example, of patients treated with fluoxetine for 1 year, 26% experienced a relapse or recurrence, in contrast to 57% on placebo (Montgomery et al., 1988). Similarly, 14% of patients treated with paroxetine relapsed or recurred versus 30% on placebo (Montgomery & Dunbar, 1993). The sertraline relapse rate over 44 weeks of continuation treatment was 13%, in contrast to 46% for placebo (Doogan & Caillard, 1992). Similarly, citalopram was significantly more effective than placebo in preventing relapse (Montgomery, Rasmussen, & Tanghoj, 1993). There are similar data for the newer SSRIs. These data are all remarkably similar and point to the efficacy of the SSRIs during continuation and maintenance treatment. Of note is that in these longer-term studies, no new side effects of the SSRIs emerged. Thus, the relative safety of this class of agents appears to be maintained after long-term treatment.

A systematic review and meta-analysis of RCTs of SSRIs versus placebo found that treatment with SSRIs is associated with symptomatic improvement (50% reduction in HAM-D score) by the end of the first week of use (Taylor et al., 2006). Dose escalation is often applied to patients who do not respond to a standard dose of an SSRI (estimated to be between 50% and 60% of patients). A systematic literature search on this practice showed that dose escalation before 4 weeks of treatment at a standard dose appeared to be ineffective (Ruhe et al., 2006). The explanation for this finding is that the occupancy of the serotonin transporter often does not increase following dose escalation. Therefore, dose escalation of SSRIs should not be recommended in treatment guidelines based on these studies. Whether some patients who are rapid metabolizers achieve suboptimal plasma levels of SSRIs and inadequate serotonin transporter blockade and would therefore benefit from dose escalation remains an unresolved area. The practice of combining other medications with an SSRI is discussed below in the section "Combination and Augmentation Therapy." SSRIs are also effective in the treatment of bipolar depression and less likely to cause a switch into mania than either TCAs or MAOIs (Nemeroff et al., 2001).

Paroxetine is a unique SSRI because it has mild anticholinergic actions and weak NE transporter inhibitory properties. These additional properties potentially explain why paroxetine has been noted to be sedating in some patients, and why it is preferred by many clinicians for patients with symptoms of anxiety. Efficacy studies of paroxetine have also been reviewed in detail by our group and others (DeBattista & Schatzberg, 1995; Herr & Nemeroff, 2004). Paroxetine was significantly more effective than placebo in 8 of 11 comparison studies in major depression. Paroxetine was comparable in efficacy to the TCAs in all but five studies, which found either the TCA or paroxetine to be more effective. Overall, dropout rates due to adverse events were lower in patients on paroxetine compared to TCAs. An early inpatient study in Denmark reported greater efficacy with clomipramine than paroxetine, and this study has been cited in the debate on SSRI efficacy in more severely depressed patients. However, this study used a relatively low dose of paroxetine (30 mg/day). Paroxetine also exists in a controlled-release form (Paxil CR) that is better tolerated by some patients.

The SSRI sertraline is unique because in addition to serotonin reuptake inhibition, at higher doses it is a DA transporter inhibitor and also binds to sigma-1 receptors. Sertraline efficacy data have been reviewed in detail by Janicak and colleagues (1993), Mendels (1995), and Shim and Yonkers (2004). Sertraline has been reported to be more effective than placebo in two large-scale clinical trials ($N = 545$) and to be of comparable efficacy to standard TCAs in two studies

(N = 320). Sertraline has also been reported to be effective in the treatment of postpartum depression (Stowe, Casarella, Landry, & Nemeroff, 1995). A systematic review and meta-analysis found that sertraline is statistically significantly superior to fluoxetine and other SSRIs as a class (Cipriani et al., 2008).

Citalopram was introduced into the U.S. market in 1998; it comprises two enantiomers (R and S). The R enantiomer has mild antihistaminic properties and is the reasons for higher-dose restrictions due to the potential for QTc prolongation. A recent FDA warning cautioned that citalopram doses exceeding 40 mg/day could cause abnormal heart rhythms, including torsades de pointes, but a large cohort study examining over 600,000 patients treated with citalopram found no elevated risk of ventricular arrhythmia compared to patients treated with sertraline (Zivin et al., 2013). In 2002, escitalopram (the S enantiomer of citalopram) was introduced. The enantiomer appears to be at least as effective as the parent compound, with potentially fewer side effects. Escitalopram is superior to citalopram in the treatment of patients with severe depression (MADRS score of 30 or more) (Llorca et al., 2005). Some have argued that alterations in the basic pharmacology, including greater effects on transporter and reuptake sites and fewer P_{450} effects, result in stronger efficacy and better tolerability for the S enantiomer, although this is still a subject of debate. Escitalopram was found to be significantly more effective than paroxetine for long-term treatment of severely depressed patients (MADRS score of 30 or more) (Boulenger et al., 2006). In this trial, patients were randomized to 24 weeks of double-blind treatment with fixed doses of either 20 mg of escitalopram (n = 232) or 40 mg of paroxetine (n = 227), and the MADRS was used to measure symptoms (Boulenger et al., 2006). This finding was also replicated by Kasper and colleagues (2009), and taken together they suggest that one should strongly consider long-term treatment with the SSRI escitalopram for severely depressed patients.

The side effects associated with increased serotonin availability and commonly seen with the SSRIs include nausea, diarrhea, insomnia, nervousness, headache, and sexual dysfunction. The first four of these are commonly dose-dependent, so that more conservative dosing frequently prevents their occurrence. Sexual dysfunction and headache are less clearly dose-related and can be observed even at low doses. The initial trials failed to report high rates of sexual dysfunction (e.g., delayed ejaculation in men and anorgasmia in women) with SSRI therapy—only 4% in an early fluoxetine trial, for example—because patients were not specifically queried about such side effects. These have become apparent with wider long-term use. It is probable that many depressed patients were not aware of or bothered by sexual dysfunction in the initial weeks of treatment but do become troubled by this side effect over time as they resume their normal activities. Currently, estimates are that at least 30% to 40% of patients on SSRIs experience adverse sexual side effects. A meta-analysis was performed to investigate the frequency of side effects induced by fluoxetine or alternative antidepressants. Fluoxetine was found to have more activating and gastrointestinal adverse effects that often required additional pharmacotherapy (Brambilla et al., 2005). It is also generally believed that SSRIs increase the risk of abnormal bleeding by blocking the uptake of serotonin into platelets, and epidemiological studies have shown that SSRI use is associated with a twofold increase in upper gastrointestinal bleeding (Andrade et al., 2010). Precautions should especially be taken with high-risk patients, particularly those with a history of gastrointestinal bleeding and those treated with nonsteroidal anti-inflammatory drugs (NSAIDs).

Because SSRIs have limited anticholinergic and noradrenergic effects, they are not cardiotoxic and are safe in overdoses. This represented a major step forward in treatment over the TCAs, which have a narrow safety margin (discussed above in the TCA section).

The SSRIs can be co-administered with the TCAs, but this needs to be done cautiously because, as a class, SSRIs generally inhibit P_{450} isoenzymes in the liver that metabolize TCAs, resulting in higher TCA blood levels and increased side effects (DeVane, 1994; Nemeroff et al., 1996). Citalopram has little effect on the activity of the cytochrome P_{450} isoenzyme. The co-prescription of SSRIs with MAOIs is generally contraindicated because of a risk of the serotonergic syndrome, characterized by myoclonic jerks, hyperpyrexia, and coma. One must also take care when switching patients from MAOIs to SSRIs (and vice versa), as previously discussed in the MAOI section.

All the SSRIs, with the exception of fluoxetine, that are marketed as antidepressants have half-lives of approximately 24 hours and can be given in a

once-a-day dose. The long half-life of fluoxetine (3 to 5 days) and its active metabolite norfluoxetine (7 to 14 days) suggests that the drug can be administered one or two times a week. Indeed, once-weekly fluoxetine has been FDA approved for the treatment of depression. Such dosing is not possible for paroxetine, citalopram, or sertraline.

Therapeutic antidepressant dosage ranges for the SSRIs are summarized in Table 11.4. The standard starting dose for fluoxetine, paroxetine, and citalopram is 20 mg/day; for sertraline, it is 50 mg/day. For most patients, 20 mg/day of fluoxetine is the therapeutic dose, with 40 mg/day the next most common dose. Some patients require higher doses (e.g., 60 to 80 mg/day), whereas others derive benefit from 10 mg/day. In double-blind studies, 20 mg/day and 40 mg/day appeared to be the most effective doses, but a 5-mg/day dose also was more effective than a placebo. (For review of dosage issues, see Schatzberg, 1995a.) Paroxetine is generally effective at doses of 20 to 30 mg/day, with a maximum recommended dose in major depression of 50 mg/day. The usual starting dose is 20 mg/day. Sertraline may be effective at 50 mg/day, but many studies report average doses of 100 to 150 mg/day. The starting dose is typically 50 mg/day and the recommended maximum dose is 200 mg/day. For citalopram, the recommended starting dose is 20 mg/day, aiming for therapeutic doses of approximately 40 mg/day; for the S enantiomer, escitalopram, the starting dose is 10 mg/day, with the recommended daily dose being 10 to 20 mg/day. There is evidence that patients who do not respond to 20 mg of escitalopram may respond to 30 or 40 mg. Paroxetine CR is dosed up to 75 mg/day. In elderly patients or for those with prominent anxiety or agitation, the recommended starting doses for SSRIs are 50% lower. To date, there are no available data that correlate antidepressant responses to SSRI plasma levels.

The abrupt cessation of an SSRI may result in a discontinuation syndrome that can mimic serious illness and can be distressing and uncomfortable to the individual. Potential symptoms of this syndrome include but are not limited to insomnia, nausea, vomiting, dizziness, headache, chills, fatigue, and myalgias. These symptoms appear within 24 to 72 hours after discontinuing an SSRI and can be alleviated by reintroducing the medication. In one RCT, fluoxetine-treated patients experienced fewer discontinuation symptoms than sertraline-treated and paroxetine-treated patients (Rosenbaum, Fava, Hoog, Ascroft, & Krebs, 1998).

SEROTONIN PARTIAL AGONIST/REUPTAKE INHIBITOR

Vilazodone was FDA approved for the treatment of depression in 2011. It is unique because in addition to acting as an SSRI, it is also a partial agonist at the $5HT_{1A}$ serotonin receptor. Human neuroimaging studies suggest that vilazodone is dosed so that about 50% of both serotonin transporters and $5HT_{1A}$ receptors are occupied (Stahl 2013). Two randomized, double-blind, placebo-controlled trials with vilazodone demonstrated its efficacy for the treatment of major depressive disorder in adults. Improvement was noted after 1 week, and it was well tolerated at a dose of 40 mg/day (Khan et al., 2011; Rickels et al., 2009). Vilazodone should be initiated at 10 mg/day and titrated to 40 mg over 2 weeks (10 mg for 7 days, then 20 mg for 7 days, and then 40 mg/day). To date, no advantage of vilazodone in terms of efficacy or tolerability in comparison with SSRIs has been demonstrated (Stahl, 2013).

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

SNRIs combine the robust serotonin reuptake inhibition of the SSRIs with various degrees of inhibition of the NE transporter. Because there is evidence that both NE and 5-HT are involved in the pathophysiology of depression and, moreover, because of evidence that both NE and 5-HT reuptake blockade is associated with therapeutic efficacy in depression, an uptake blocker of both monoamines was considered of interest, especially if such a drug lacked the adverse side-effect profile of the TCAs. Additionally, the inhibition of NE transporters in the prefrontal cortex increases the availability of DA in this area of the brain because DA presynaptic terminals in the prefrontal cortex lack DA transporters. The DA released in this region is not inactivated until it is degraded by the enzyme catechol-*O*-methyl-transferase or until it is taken up by the NE transporter (Stahl, 2013). When SNRIs inhibit NE transporters, DA levels in the prefrontal cortex increase. Currently there are four SNRIs approved for major depressive disorder in

the United States: venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran, the latter approved in July 2013. Milnacipran is currently approved in the United States for the treatment of fibromyalgia but not depression.

Venlafaxine produces different degrees of inhibition of serotonin and NE reuptake depending on dose. Its serotonergic actions are present at low doses, while its noradrenergic actions are progressively enhanced as the dose increases (Stahl, 2013). Unlike TCAs, venlafaxine produces no orthostatic hypotension, dry mouth, constipation, blurry vision, or sedation. Its side-effect profile is exactly what one would predict from its postulated mechanism of action, namely the combination of the SSRIs' side effects (nausea, headache, sexual dysfunction, and insomnia) and the NE reuptake blockers' side effects (hypertension, tachycardia, and sweating). The original preparation was associated with considerable nausea, but this has been partly obviated with the introduction of an ER formulation. The starting dose is 75 mg/day, and although this is an effective dose in some patients, most require doses of up to 225 mg/day or even higher (Table 11.5). Another major advantage of venlafaxine is its lack of inhibition of any of the cytochrome P_{450} hepatic isoenzymes responsible for drug–drug interactions with certain of the SSRIs (see the introductory section of this chapter). This allows for the combination of venlafaxine with other medications in nonresponsive patients. Venlafaxine is proconvulsant in overdose and thus should not be prescribed to a patient at risk for seizures (Whyte, Dawson, & Buckley, 2003). Additionally, compared to TCAs, venlafaxine overdose is more likely to cause serotonin toxicity but less likely to cause coma (Whyte et al., 2003). It is also more lethal in overdose than SSRIs, as described in the British Behavioral Health Science database (Whyte et al., 2003).

TABLE 11.5 Atypical Antidepressants

Drug		
Generic Name	*Trade Name*	*Dose Range (mg/day)*
Trazodone	Desyrel	300–600
Nefazodone*	Serzone*	400–600
Bupropion	WellbutrinXL**	150–300**
Venlafaxine	Effexor	75–300
Venlafaxine ER	Effexor XR	75–225
Mirtazapine	Remeron	30–45
Duloxetine	Cymbalta	60–120
Levomilnacipran	Fetzima	40–120

*Serzone trade named product not currently available. Generic nefazodone is available.

**Also available as Wellbutrin and Wellbutrin SR with upper dose limitations of 450 mg and 400 mg/day, respectively.

Venlafaxine has a short half-life, so it attains steady-state plasma levels very rapidly compared with other antidepressants. This has led to the question of whether venlafaxine is superior to SSRIs in attaining remission rates in patients. Indeed, data from eight comparable randomized, double-blind studies showed that remission rates were significantly higher with venlafaxine (45%) than with an SSRI (35%) (Thase, Entsuah, & Rudolph, 2001). The difference between venlafaxine and the SSRIs was significant at week 2, whereas the difference between the SSRIs and the placebo did not reach significance until week 4 (Thase et al., 2001).

Venlafaxine may be more effective than the SSRIs in severe depression (frequently defined as the melancholic subtype or the endogenous subtype) as well as in hospitalized depressed patients. Two early double-blind controlled studies evaluated the efficacy of venlafaxine for severe depression. In one (Guelfi, White, Hackett, Guichoux, & Magni, 1995), venlafaxine was shown to be effective for severe depression compared with placebo; most impressive was the lack of any effect of the placebo in this population. In a second study (Clerc et al., 1994), fluoxetine and venlafaxine were compared in depressed inpatients; both drugs were effective, but venlafaxine was more effective than fluoxetine, and its antidepressant effect had a more rapid onset of action. Another interesting finding from the EPIC 014 Study (Nemeroff & Thase, 2007) was that venlafaxine is superior to placebo on most outcome measures, whereas the differences between fluoxetine and placebo are not as consistent. Nemeroff and colleagues (2008) reviewed 34 studies and reported that venlafaxine appears to be statistically superior to SSRIs as a class in major depression, but only to fluoxetine individually. Sertraline and venlafaxine ER have comparable effects on quality of life and efficacy in treatment, but sertraline has a reduced risk of blood pressure increase (Shelton et al., 2006; Sir et al., 2005).

Additionally, venlafaxine ER is more effective than fluoxetine and paroxetine for sustaining remission of depressive symptoms (Shelton, Entsuah, Padmanabhan, & Vinall, 2005), and as previously discussed in the introduction, venlafaxine ER is efficacious and safe as maintenance therapy for patients with recurrent unipolar depression.

Venlafaxine is a substrate for cytochrome P_{450} 2D6, which converts it to the active metabolite desvenlafaxine. Desvenlafaxine is a more potent NE transporter inhibitor than a serotonin transporter inhibitor as compared to venlafaxine (Stahl, 2013). Desvenlafaxine was recently FDA approved for the treatment of depression. It is superior to placebo in the short-term treatment of depression (DeMartinis, Yeung, Entsuah, & Manley, 2007); and, similar to venlafaxine, desvenlafaxine at the recommended dose of 50 mg/day is effective in relapse prevention of depression (Rickels et al., 2010; Rosenthal, Boyer, Vialet, Hwang, & Tourian, 2013). The safety and tolerability of desvenlafaxine have been proven to be consistent with those of the SNRI class (Clayton, Kornstein, Rosas, Guico-Pabia, & Tourian, 2009). To date, there is no evidence that desvenlafaxine is more effective or better tolerated than its parent compound, venlafaxine.

Duloxetine is similar in structure to fluoxetine but, unlike the latter, it blocks both NE and serotonin reuptake (the serotonin reuptake inhibition being slightly more potent). The drug, which was introduced in the United States in 2004, is approved for major depression, as well as for diabetic neuropathic pain, generalized anxiety disorder, fibromyalgia, and chronic musculoskeletal pain. It is now widely appreciated that painful physical symptoms are frequently associated with depression. As a dual uptake inhibitor, duloxetine appears to enhance the filtering of pain signals and to decrease the chronic physical pain often seen in depression. Its side-effect profile is similar to those of SSRIs, with nausea being perhaps the most common adverse event, occurring in as many as 40% of subjects started at 60 mg/day. There are data suggesting that starting duloxetine at 20 mg in the morning for 1 week with or without food, or starting it at 60 mg in the morning with food can improve the initial tolerability of the medication (Whitmyer et al., 2007).

Duloxetine has been reported to be significantly more effective than placebo at 60 mg/day (Detke, Lu, Goldstein, McNamara, & Demitrack, 2002; Goldstein, Mallinckrodt, Lu, & Demitrack, 2002), and its efficacy does not differ significantly in male and female patients (Kornstein, Wohlreich, Mallinckrodt, Watkin, & Stewart, 2006). Duloxetine 60 mg/day is as effective as 120 mg/day dose in treating severe depressive symptoms in hospitalized patients (Brecht et al., 2011). Patients who do not obtain remission (HAM-D-17 score of more than 7) after 6 weeks of duloxetine 60 mg/day can obtain symptom improvement if they continue on the drug, but there is no difference in improvement between those kept on a 60-mg/day dose and those whose dosage is increased to 120 mg/day (Kornstein et al., 2008). Duloxetine has also been shown to be effective in preventing relapse during maintenance/continuation treatment and in providing better global well-being and quality of life when compared to placebo (Perahia et al., 2006, 2009). Duloxetine has been compared to escitalopram in two studies, both of which showed similar efficacy between the drugs (Khan et al., 2007; Pigott et al., 2007). Escitalopram does have an advantage over duloxetine, though, in improving sleep and in tolerability measures (Pigott et al., 2007). In two studies sponsored by the manufacturer of duloxetine, Eli Lilly, venlafaxine was superior in efficacy to duloxetine (www.lillytrials.com).

Levomilnacipran was approved by the FDA for the treatment of major depressive disorder in July 2013. On the basis of in vitro studies, it is the SNRI with the greatest effect on the NE transporter (Auclair et al., 2013). A phase 3 trial showed that levomilnacipran sustained-release (SR) provides significant improvement in depressive symptoms and functioning compared to placebo (Asnis, Bose, Gommoll, Chen, & Greenberg, 2013). The dosage range of this drug is 40 to 120 mg/day. Patients should be instructed to take 20 mg for the first 2 days and then increase the dose to 40 mg. The daily dose can be increased in increments of 40 mg/day at intervals of 2 or more days, never exceeding 120 mg/day.

NOREPINEPHRINE-DOPAMINE REUPTAKE INHIBITORS

Bupropion differs from many of the other antidepressants discussed because it does not have substantial serotonergic activity. Its exact mechanism of action remains obscure. It is a very weak inhibitor of both DA and NE uptake (Eshleman et al., 1999).

Like the other antidepressants, the efficacy of bupropion in the treatment of major depression is

comparable to that of TCA and fluoxetine. Bupropion was introduced in immediate-release form with three-times-daily dosing, but this was associated with an increased incidence of seizures in patients with a history of bulimia or head injury. A twice-a-day formulation (bupropion SR) reduced the frequency of seizures at peak plasma drug levels and enhanced adherence. Actually, the once-a-day dosing formulation (bupropion XL) has a risk of seizures no greater than that observed with other antidepressants.

Bupropion has certain advantages over TCAs, including a lack of orthostatic hypertension, few cardiovascular effects, and no anticholinergic effects. Bupropion produces no sedation or cognitive impairment and, most important, in contrast to the SSRIs it produces no sexual dysfunction. It has similar HAM-D-17 remission rates to that of escitalopram (Clayton et al., 2006). There is no statistically detectable difference in the onset of antidepressant effect between bupropion and the SSRIs (Papakostas et al., 2007). Thus, bupropion is a reasonable first-line choice and a particularly useful antidepressant for patients who cannot tolerate the serotonergic side effects of SSRIs or for those who do not respond to SSRIs. In contrast to the TCAs, which are well known to produce weight gain, treatment with bupropion is either weight-neutral or results in weight loss in many patients.

Bupropion appears to be especially useful in targeting the symptoms of "reduced positive affect" (loss of interest, pleasure, energy) (Jefferson et al., 2006). Because of its activating/stimulating property, bupropion is rarely prescribed by physicians when a patient has comorbid anxiety disorder or symptoms of CNS activation (Zimmerman et al., 2005). However, there are considerable data indicating that it is just as effective as SSRIs in treating patients with depression and prominent anxiety symptoms. It is prescribed more than other antidepressants when the desire to avoid side effects, especially sexual dysfunction and weight gain, is the priority (Zimmerman et al., 2005). Lastly, bupropion SR, sertraline, and venlafaxine ER are all equally reasonable second-step choices for patients with depression who have failed to respond to treatment with an SSRI (Rush et al., 2006).

SEROTONIN ANTAGONIST/REUPTAKE INHIBITORS

Trazodone and nefazodone fall into this category of antidepressants because they block serotonin 2A and 2C receptors, as well as weakly inhibit the reuptake of serotonin. Due to this unique dual mechanism, what happens when trazodone raises serotonin levels is different from what happens when SSRIs and SNRIs increase them. Specifically, the blocking action of these drugs on the 2A and 2C receptors results primarily in stimulation of the serotonin 1A receptors only and likely explains why the drugs are not associated with sexual dysfunction or insomnia/anxiety (Stahl, 2013).

Trazodone is an interesting drug because it acts differently at different doses. At low doses, it causes sedation and is an effective treatment of insomnia. Because insomnia is one of the most frequent residual symptoms of depression during treatment with an SSRI, sedative-hypnotics are often necessary for patients with a major depressive episode (Stahl, 2013). Therefore, the sedating property of trazodone may be one important mechanism whereby trazodone can augment the efficacy of other antidepressants. The antidepressant properties of trazodone are not observed until higher doses are prescribed. Additionally, trazodone has a short half-life of 3 to 9 hours, requiring multiple daily doses. Trazodone is usually initiated at a dosage of 100 to 150 mg/day and is increased to a dosage of 400 to 600 mg/day to obtain optimal antidepressant effects. Although these doses can be administered once per day, usually at bedtime, they are often administered in divided doses, particularly when the dosage exceeds 300 mg/day.

Several RCTs have revealed that trazodone is as effective as TCAs and fluoxetine in the treatment of major depression (Schatzberg, 1987), although many clinicians have the impression that it is not as effective in moderate to severe depression.

Nefazodone is not commonly used because of the very rare emergence of severe hepatotoxicity and a need for liver transplantation, seen in 1/250,000 exposures. This resulted in the manufacturer ceasing production, although a generic form is still available. Nefazodone is an inhibitor of the cytochrome P_{450}-3A4 isoenzyme. If prescribed, caution should be used if combining it with benzodiazepines such as alprazolam, triazolam, or midazolam because they are also metabolized by the same enzyme. When they are co-administered with nefazodone, marked elevation of plasma concentrations can occur. Similar drug–drug interactions can occur when nefazodone is co-prescribed with protease inhibitors used in the treatment of HIV/AIDS.

The major side effect of this class of drug is sedation, but as previously mentioned, they can be used in combination with SSRIs and SNRIs to treat persistent insomnia. These drugs have fewer anticholinergic side effects than TCAs, but a primary drawback, particularly in the elderly, is orthostatic hypotension, thought to be due to α_1-adrenergic receptor blockade. Another potentially serious adverse side effect of trazodone particularly is the fact that a small percentage of men develop priapism after trazodone use; in a small percentage of those individuals, surgical intervention is necessary. Trazodone has also been associated with arrhythmias in patients with preexisting cardiac disease.

ADRENERGIC RECEPTOR ALPHA-2 ANTAGONISM

Alpha-2 adrenergic antagonism is another way to enhance the release of NE and serotonin and theoretically exert an antidepressant effect. Currently, there is no selective α_2 antagonist available for use as an antidepressant, but mirtazapine has prominent α_2 antagonist properties. In addition to its α_2 antagonism action, it is also a $5HT_{2A}$, $5HT_{2C}$, and $5HT_3$ receptor and an H_1 receptor antagonist. Its major advantages include a single daily dose, the lack of sexual dysfunction, safety in overdose, and sedating properties; the latter is particularly helpful in depressed patients with profound insomnia, as often seen in elderly patients. Its major side effects include marked daytime somnolence, to which patients eventually become tolerant, as well as increased appetite, weight gain, and dizziness. Of 2,796 patients in clinical trials, 2 developed agranulocytosis and 1 developed severe neutropenia. Wide-scale use after release has not revealed an increased risk of this reaction. The drug has become commonly used in geriatric patients, where sedation is a potential benefit and in whom weight gain is less common (Schatzberg, Kremer, & Rodrigues, 2002). Its efficacy has been reported to be faster and slightly greater than that of the SSRIs and SNRIs in several studies (Benkert, Szegedi, & Kohnen, 2000; Benkert et al., 2006; Schatzberg et al., 2001). Actually, a recent meta-analysis of 15 controlled trials reported that mirtazapine-treated patients had a 74% higher likelihood of achieving remission during the first 2 weeks of therapy compared to patients treated with SSRIs (Thase et al., 2010). Additionally, mirtazapine has been shown to be effective in SSRI nonresponders (Thase, Kremer, & Rodrigues, 2001).

SEROTONIN MODULATING AGENTS

Vortioxetine is a multimodal antidepressant that was just approved by the FDA for the treatment of major depressive disorder. It is a serotonin $5HT_3$, $5HT_7$, and $5HT_{1D}$ receptor antagonist; a serotonin $5HT_{1B}$ receptor partial agonist; a serotonin $5HT_{1A}$ receptor agonist; and an inhibitor of the serotonin transporter (Alvarez, Perez, Dragheim, Loft, & Artigas, 2012). In one study, patients with a MADRS total score of at least 30 were randomized to receive (1) 5 or 10 mg of vortioxetine; (2) placebo; or (3) 225 mg of venlafaxine XR (Alvarez et al., 2012). Vortioxetine was superior to placebo at week 6 in change from baseline MADRS total score (Alvarez et al., 2012). It was not superior to venlafaxine, however. A more recent study of vortioxetine 5 mg versus placebo found no statistically significant difference between the two groups in change from baseline in HAM-D at the end of 6 weeks (Jain, Mahableshwarkar, Jacobsen, Chen, & Thase, 2013). Additional positive trials have now been realized.

SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS

The first truly SNRI marketed in Europe and other countries is reboxetine; the first in the United States is atomoxetine. Reboxetine is approved for the treatment of major depressive disorder in Europe, but not in the United States. In an RCT with reboxetine 4 mg twice daily and citalopram 20 mg daily, reboxetine did not confer any advantage over citalopram in Beck Depression Inventory total scores after 6 weeks of treatment (Wiles et al., 2012). Atomoxetine is currently approved only for the treatment of attention-deficit/hyperactivity disorder (ADHD) in the United States.

MELATONIN AGONIST

There is growing evidence that depression is associated with altered circadian rhythm of patients, causing a phase delay in their sleep/wake cycle (Stahl, 2013). This can have a negative effect on many organ systems and in particular on melatonin secretion.

Agomelatine is an agonist at melatonin 1 and 2 receptor subtypes and is approved as an antidepressant in many countries outside of the United States. By stimulating melatonin receptors, this drug appears to resynchronize circadian rhythms, reverse the phase delay of depression, and exert an antidepressant effect (Stahl, 2013). Additionally, agomelatine is an antagonist at serotonin $5HT_{2C}$ receptors, which is believed to contribute to its antidepressant effects. A recent meta-analysis of all acute treatment studies reported a modest mean difference from placebo of approximately 1.5 points on the HAM-D (Koesters et al., 2013). This same meta-analysis, though, reported that data extracted from three relapse prevention studies failed to show significant effects of agomelatine over placebo. Since the negative trials of agomelatine have not been published, a clinically important difference between agomelatine and placebo may be unlikely.

COMBINATION AND AUGMENTATION THERAPY

Frequently, patients exhibit only partial or no response to antidepressant monotherapy. These patients with treatment-resistant depression (commonly defined as treatment failure on two antidepressants) often benefit from combination or augmentation therapy. Combination therapy is the practice of prescribing two antidepressants from different classes; augmentation therapy is the addition of a pharmacological agent that is not itself an antidepressant but increases the efficacy of antidepressants. There is a vast literature on these two treatment strategies, and some of the major findings are described here.

There is evidence suggesting that antidepressant combinations (mirtazapine plus fluoxetine, mirtazapine plus venlafaxine, mirtazapine plus bupropion) from treatment initiation may double the likelihood of remission (HAM-D score of less than 7) compared with fluoxetine monotherapy (Blier et al., 2009). These drug combinations are believed to work because they modulate all three monoamines (serotonin, DA, and NE). The combination of citalopram with sustained-release bupropion has also appeared useful in clinical settings (Trivedi et al., 2006). It must be noted, though, that another clinical trial demonstrated no benefit of combination antidepressant therapy over monotherapy in patients with chronic and/or recurrent major depressive disorder (Rush et al., 2011). In this study, patients received escitalopram plus placebo, sustained-release bupropion plus escitalopram, or extended-release venlafaxine plus mirtazapine. There was no significant difference in remission rates among the treatment groups at 12 weeks.

Multiple agents have been investigated for augmentation use in treatment-refractory depression. Adjunctive S-adenosyl methionine (SAMe) and L-methylfolate have both been reported to be effective and well tolerated in patients who are nonresponders to SSRIs (Papakostas et al., 2010, 2012). Lithium has been studied as both an augmenting agent and an accelerating agent. There is firm evidence that it is effective when used as an augmentation agent, but it does not accelerate response to antidepressants (Crossley & Bauer, 2007). Lithium and T3 augmentation were compared in the STAR-D trial, and although their remission rates did not differ significantly, the lower side-effect burden of T3 suggests that it might have a slight advantage over lithium (Nierenberg et al., 2006). Other studies have reached conflicting conclusions about whether T3 augmentation is a promising treatment strategy in SSRI-resistant depression (Iosifescu et al., 2005; Garlow, Dunlop, Ninan, & Nemeroff, 2012). Creatine augmentation of SSRI treatment may be a promising therapeutic approach that has shown efficacy in women and should be further investigated (Lyoo et al., 2012).

Atypical antipsychotics, such as olanzapine, risperidone, quetiapine, and aripiprazole, have been studied extensively as augmentation agents and have clear efficacy in this regard (Papakostas et al., 2005; Rapaport et al., 2006; Simon & Nemeroff, 2005; Thase et al., 2007). Indeed, data from 10 clinical trials of adjunctive treatment with an atypical antipsychotic agent revealed that the patients randomized to adjunctive treatment were more likely to experience remission when compared to placebo (Papakostas, Shelton, Smith. & Fava, 2007). Data from a pilot study also showed that risperidone is beneficial as an augmenting treatment for patients who develop high-risk suicidal ideation during a depressive episode (Reeves et al., 2008). Further larger-scale investigation is warranted. Recently, oral scopolamine was administered as an augmentation agent and was found to be safe and effective, showing higher rates of response and remission than placebo (Khajavi et al., 2012). Other agents, such as pindolol and atomoxetine, have been

studied but have not demonstrated any clear benefit (Geretsegger et al., 2008; Michelson et al., 2007). The role of omega-3 fatty acids is another strategy that has produced mixed results and requires further study.

UNDER INVESTIGATION

Amitifadine is a serotonin, NE, and DA reuptake inhibitor that is most potent at the serotonin transporter. In one study with 63 patients, 6 weeks of treatment significantly improved MADRS total score versus placebo (Richelson, 2013).

An interesting development in recent years has been the observation that an intravenous infusion of a subanesthetic dose of ketamine, a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist, can exert an immediate antidepressant effect and reduce suicidal thoughts in patients with treatment-resistant depression. A preliminary study of 14 depressed patients with suicidal ideation in the emergency department showed improvement in MADRS scores following a single intravenous bolus of ketamine (Larkin & Beautrais, 2011). A more recent study randomly assigned patients with treatment-resistant depression to a single intravenous infusion of ketamine or midazolam and measured the change in depression severity 24 hours after drug administration with the MADRS (Murrough et al., 2013). Patients in the ketamine group had greater improvement in the MADRS score than the midazolam group. Further studies are needed to better understand the role that ketamine and related compounds may play in the treatment of major depression and to gain more information on response duration and safety.

HOW TO CHOOSE AN ANTIDEPRESSANT

Currently, there is little evidence for superiority of one treatment option over another. An increasingly popular approach to selecting an antidepressant is basing the decision on the patient's specific symptoms (e.g., decreased interest, problems concentrating, insomnia). Using this approach, a patient's specific individual symptoms of depression are matched with the brain circuits that hypothetically mediate them and a treatment with the appropriate neuropharmacological mechanism is chosen. Although of considerable heuristic value, the data obtained thus far have not, with few exceptions such as atypical depression, supported this approach.

There is one general treatment principle that is agreed upon, and this is when to switch a medication versus when to augment it. A new medication should be prescribed when the first treatment is not tolerated because of side effects of if the patient shows absolutely no response after an appropriate trial at an adequate dose. In contrast, antidepressant monotherapy should be augmented with a second antidepressant or augmenting agent if the patient exhibits a partial response.

DISCUSSION

For all antidepressants available in the United States, efficacy has been clearly demonstrated in double-blind, placebo-controlled RCTs. The differences among these classes of agents revolve primarily around their side effects and safety. The first-generation TCAs and MAOIs are less well tolerated and are more dangerous in overdose than are the newer agents. For this reason alone, the SSRIs and other newer agents represent an incremental advance in the treatment of major depression. Moreover, the TCAs are largely noradrenergic in their reuptake blocking effects, exerting less effects on serotonin reuptake (with clomipramine a notable exception). The difference in monoamine reuptake blockade most likely accounts for the broad range of efficacy for the SSRIs (e.g., panic, OCD, bulimia, premenstrual syndrome) as well as for their salutary effects in milder forms of depression, such as dysthymia.

Although the various classes enjoy efficacy for major depression, a number of issues about their relative efficacy for specific subgroups or subtypes of depression remain in debate. For example, as indicated earlier, some argue that the TCAs are more efficacious and are more likely to induce remission in melancholic depressives than the SSRIs. Another issue is whether the MAOIs (and perhaps the SSRIs) are more effective in atypical depressives than are the TCAs. These areas require further RCTs.

The relatively high placebo response rates in outpatient studies are of concern because both known and investigational antidepressants have failed to separate from placebo. Research and clinical experience suggest more severely ill patients exhibit a

lower placebo response rate, but they also show poorer response to active drug. Thus, including more severely ill patients to address this issue is not a perfect solution. As indicated in the introduction, we need to clarify what placebo treatment in a study actually represents. Certainly, the supportive hand-holding and patient contact that occur in clinical trials do not really reflect a no-treatment condition but instead constitute potentially powerful interventions. Novel study designs are urgently needed to test drug efficacy.

Although many issues remain regarding the range of efficacy for antidepressants, these drugs are certainly effective in patients with major depression, and their use has had a tremendous impact on the lives of many depressed patients.

DISCLOSURES

Dr. Nemeroff currently has research grants from the National Institutes of Health (NIH) and consults to Xhale, Takeda, SK Pharma, Shire, Roche, Lilly, Allergan, Mitsubishi Tanabe Pharma Development America, Taisho Pharmaceutical Inc., and Lundbeck. He is a stockholder of CeNeRx BioPharma, PharmaNeuroBoost, Revaax Pharma, and Xhale and has other financial interests with CeNeRx BioPharma and PharmaNeuroBoost. He is on multiple advisory boards: American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma (2012), National Alliance for Research on Schizophrenia and Depression (NARSAD), Xhale, PharmaNeuroBoost (2012), Anxiety Disorders Association of America (ADAA), and Skyland Trail. He is on the following Board of Directors: AFSP, NovaDel (2011), Skyland Trail, Gratitude America, and ADAA. He has income sources or equity of $10,000 or more in PharmaNeuroBoost, CeNeRx BioPharma, NovaDel Pharma, Reevax Pharma, American Psychiatric Publishing, and Xhale. He currently has patents for method and devices for transdermal delivery of lithium (US 6,375,990B1) and method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2). Lastly, he has various honoraria and royalties.

Dr. Schatzberg currently consults to Bay City Capital, CeNeRx, Cervel, Eli Lilly, Genentech, Gilead, Lundbeck, Takeda, McKinsey, Merck, MSI, Neuronetics, PharmaNeuroBoost, and Xhale. He has equity in Amnestix, BrainCells, Cervel, Corcept (co-founder), Delpor, Forest, Merck, Neurocrine, Pfizer, Titan, and Xhale. Lastly, he is Named Inventor on pharmacogenetic and antiglucocorticoid use patents on prediction of antidepressant response.

Dr. Prendes-Alvarez has no disclosures.

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12

Treatments for Pediatric Depression

Carolina Biernacki
Prerna Martin
Pablo H. Goldberg
Moira A. Rynn

Practice guidelines recommend psychosocial interventions for mild or brief cases of pediatric depression. In moderate to severe cases, medication treatment is recommended, with or without cognitive-behavioral therapy (CBT). Currently, fluoxetine and escitalopram are the only antidepressants approved by the U.S. Food & Drug Administration (FDA) for acute pediatric depression. Among psychosocial interventions, CBT and Interpersonal Psychotherapy for Adolescents (IPT-A) have the largest evidence base for treatment of depressed youth. Combination treatment with CBT and antidepressant medication is superior to treatment with either modality alone. In youths with treatment-resistant depression, a switch in antidepressant is more likely to yield a positive response when medication is used with CBT. Antidepressant use in youths should remain judicious as higher rates of adverse events have been demonstrated, and data from adult medication trials cannot be systematically extrapolated to the pediatric population. Further studies are needed to continue assessing alternative medication and psychosocial treatments as well as factors predictive of treatment response.

BACKGROUND

Major depressive disorder (MDD) is one of the more common psychiatric disorders of adulthood, known to affect primarily one's mood and motivation. However, the symptoms that define depression result in a wide range of dysfunction, causing significant morbidity, including the possibility of leading to suicide. Children and adolescents diagnosed with MDD present similarly to adults, with some differences that have been attributed to their physical, emotional, cognitive, and social developmental stage (Birmaher et al., 1996; Lewinsohn et al., 2003; Yorbik et al., 2004). Depressed school-aged children tend to present with "typical" depressive symptoms and display fewer "masked" symptoms such as sleep or appetite disturbance (Luby et al., 2003). Irritability, behavioral manifestations, and somatic symptoms are more commonly seen in children and adolescents than in adults, whereas melancholic symptoms, delusions, and suicide attempts are less common in children than in teens and adults (Birmaher et al., 2007). The presence of psychotic symptoms in depressed youths has also been associated with an increased risk of bipolar disorder later in life, which is not the case in adults with psychotic depression (Strober & Carlson, 1982).

Epidemiology and Risk

Epidemiological data show that approximately 8% of children and adolescents experience depression

worldwide (Eapen & Črnčec, 2012), with an increasing risk of diagnosis with age. By the time youths reach 18 years of age, 11% of them are affected (Merikangas et al., 2010), with a 2:1 female: male ratio above the age of 15 years (Hankin et al., 1998). Recurrence of depression is common, with a rate of 50% in one's lifetime and up to 70% within 5 years of the initial episode (Kessler et al., 2001; Kovacs et al., 1984). In fact, according to the World Health Organization, the leading cause of disability among Americans between the ages of 15 and 44 years is MDD (Mathers et al., 2008). In children and adolescents, the burden of illness manifests itself with severe impairment in at least one major domain such as home, school or work, family relationships, and social life (SAMHSA, 2012) and leads to an increased risk of early pregnancy, legal problems, substance abuse, and suicide (Sakolsky & Birmaher, 2012). An inverse relationship between chronicity and response has been established, making early diagnosis and treatment more likely to lead to improved outcomes (Bridge et al., 2007; Rey & Birmaher, 2009). It is therefore crucial for early diagnosis and systematic treatment to become the rule rather than the exception, with the hope of preventing future morbidity and mortality.

Current vulnerability models focus on the interplay between genes and environment; however, such models are challenging to study, and results have been difficult to reproduce (Brzustowicz & Freedman, 2011). Biological risk has nevertheless been well established. Monozygotic twin concordance rates vary between 40% and 60% (Todd & Botteron, 2001), while first-degree relatives show a two- to four-fold increase in depression, both from parents to children and vice versa (Weissman et al., 2005). Actual biological mechanisms are less clear, although pubertal hormonal changes have been implicated, particularly in girls (Angold et al., 1999). Broader factors pertaining to one's ability to self-regulate emotions seem to be at play, with an increased risk of depression in children who experience less positive affectivity, less mood repair, and impaired functioning in the hypothalamic-pituitary-adrenal (HPA) axis and cerebral and vagal systems (Kovacs & Lopez-Duran, 2010). Environmental factors have been shown to be at least as important as genetic predisposition, with poverty, stressful life events, maltreatment by caregivers or peers, parental mental illness, and low family cohesion increasing the likelihood of depression (Gilman et al., 2003; Jaffee et al., 2002). In addition, cognitive vulnerabilities in children and adolescents can lead to depression (Kendall et al., 1990). Overall, it appears that youths with a higher genetic vulnerability, as represented by relatively higher negative affectivity, may require only a small environmental insult to develop depression. Youths with less genetic predisposition would likely develop the disorder only in the context of a major environmental stressor (Brzustowicz & Freedman, 2011).

Diagnostic Criteria

The diagnostic criteria in the various iterations of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) have not distinguished between MDD in adults and its manifestation in children and adolescents (American Psychiatric Association [APA], 2013). The criteria remain mostly the same in today's *DSM-5* and continue to be used for children and adolescents. They consist of depressed mood and/or loss of interest or pleasure in life activities for at least 2 weeks, along with five or more of the following symptoms causing significant impairment in functioning: (1) depressed mood for most of the day nearly everyday—mood can be irritable in children/adolescents, (2) diminished interest or pleasure in usual activities, (3) significant weight loss or gain that is unintentional, (4) insomnia or increased sleep, (5) agitation or psychomotor retardation, (6) fatigue or low energy, (7) feelings of worthlessness or guilt, (8) difficulty concentrating or indecisiveness, and (9) recurrent thoughts of death or suicide. Two specifiers ("with anxious distress" and "with mixed features") have been added to the diagnosis, while the bereavement exclusion has been removed (APA, 2013). A new diagnosis of premenstrual dysphoric disorder, which was previously mentioned in the appendix of the *DSM-IV*, has also been included in the depressive disorders category. When discussing treatment of depressive disorders or "depression" in youths, one would previously be referring to MDD and dysthymic disorder (DD). However, *DSM-5* has brought about interesting and important changes in this category, establishing a new diagnosis of disruptive mood dysregulation disorder (DMDD) in children and adolescents. The presence of persistent, severe, and pervasive symptoms differentiates these children and adolescents from merely temperamental youths or those diagnosed with oppositional defiant

disorder (ODD) (APA, 2013). The diagnostic criteria do include an age range between 6 and 18 years old outside of which a diagnosis of DMDD cannot be made, and initial symptoms must be present prior to age 10. The criteria further require chronic and severe temper outbursts, verbal aggression, or emotional storms that are disproportionate to the situation and occur at least three times a week over a period of 12 months; persistent irritability that does not remit between episodes or when stressors go away; irritability that is observed in two out of three settings (home, school, with peers) and is severe in at least one of them; no prior diagnosis of mania or euphoric mood for more than 1 day; and no other disorder (psychiatric, medical, or neurological) that could result in or better account for such behavior (APA, 2013).

Extensive research has shown that children exhibiting symptoms now ascribed to DMDD are at risk of developing MDD or generalized anxiety disorder (GAD) later in life (APA, 2013). These children were previously being diagnosed with bipolar disorder (BD), suggesting a more worrisome prognosis and possibly misguiding their treatment. Although the new diagnosis of DMDD hopes to address the overdiagnosis of BD and warrants more appropriate treatment for these youths, there are little to no research data providing DMDD-specific treatment guidelines, leaving us to abide by the guidelines set forth for MDD. A further change brought about by the *DSM-5* is the inclusion of DD and chronic MDD in a "persistent depressive disorder" category, as scientific research could not distinguish between the two diagnoses in a meaningful way (APA, 2013). The duration criteria for children remain unchanged at 1 year (vs. 2 years for adults), with an early-onset specifier to be given if a diagnosis is made prior to the age of 21. There is similarly very little research aimed at the pharmacological treatment of dysthymia or persistent depressive disorder in children and adolescents. We will therefore include all three diagnoses—MDD, DMDD, and persistent depressive disorder—when discussing treatment for "depression" in youths. The diagnosis itself is usually made by clinical interviews with the parent(s) and child separately. Collateral information from school staff can be useful if available, and contextual factors should be explored (e.g., peer relationships, family stressors). Comorbid conditions should be assessed for, since the presence of additional diagnoses will influence treatment approaches. Various rating scales can also be used to assess the initial severity of symptoms and monitor improvement or worsening of symptoms during treatment. These scales include the clinician-rated Children's Depression Rating Scale-Revised (CDRS-R), Clinical Global Impression-Improvement (CGI-I), Hamilton Depression Rating Scale (HAM-D), and Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C_{16}), as well as self-reports like the Beck Depression Inventory (BDI), Children's Depression Inventory (CDI), Mood and Feelings Questionnaire (MFQ), Patient Health Questionnaire (PHQ-9), Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR_{16}), and Reynolds' Adolescent Depression Scale—2nd Edition (RADS-2) (Choe et al., 2012).

PRACTICE GUIDELINES AND TREATMENT RECOMMENDATIONS

In light of the robust placebo response seen across pediatric depression medication trials (Cohen et al., 2008), practice guidelines recommend that antidepressant treatment be reserved for patients with moderate to severe depression (Birmaher et al., 2007; Bridge et al., 2007, 2009; Curry et al., 2006). Supportive treatment and education are recommended as first-line treatment for youths with uncomplicated, brief, or mild depression, as symptoms can be reduced in as little as 1 to 4 weeks (Birmaher et al., 2007; Cheung et al., 2007; Hughes et al., 2007). If symptoms do not respond, a trial of psychotherapy, medication management, or both can be initiated. For children and adolescents with depressive symptoms that are chronic or recurrent, that are moderate or severe, or that occur in the presence of agitation, psychosis, suicidality, or considerable functional impairment, a trial of a specific type of psychotherapy and/or antidepressant medication is recommended (Birmaher et al., 2007). Current psychotherapy modalities with the strongest evidence base for depressed children and adolescents are CBT and Interpersonal Psychotherapy (IPT). These, along with other modalities, will be discussed in the psychosocial treatment section of this chapter. Psychotherapy can be initiated before trying medication, or medication can be started first as it can begin to alleviate symptoms more quickly and help youth become more amenable to psychotherapeutic treatment. If neither modality produces a response on its own, they should

both be implemented simultaneously (Birmaher et al., 2007).

Once the need for a medication trial is established, treatment proceeds in the usual sequence recommended for adults, which consists of the acute phase, the continuation phase, and the maintenance phase. The goal of the acute phase is remission or maximal response of symptoms. As will be discussed in a later section, most antidepressant trials for pediatric depression have only examined the acute phase of treatment spanning 8 to 12 weeks, and they have shown mostly modest efficacy. The continuation phase, which aims to consolidate the acute phase as well as relapse prevention, should last at least 6 months (Birmaher et al., 2007). In fact, the follow-up treatment phase for acute treatment trials such as the Treatment of Adolescent Depression Study (TADS; TADS Team, 2007) and the Treatment of Resistant Depression in Adolescents Study (TORDIA; Brent et al., 2008) showed further improvement in response rates when subjects received continuation treatment with medication and/or CBT (Emslie et al., 2010; TADS Team, 2007). Maintenance treatment has yet to be studied thoroughly in children and adolescents, but naturalistic follow-up of adolescents after completion of acute and continuation phases has revealed further improvement in symptoms (Curry et al., 2011; Kennard et al., 2009; Vitiello et al., 2011). The goal of the maintenance phase is to prevent recurrence of depression for at least 12 months following recovery from an acute episode. Current pediatric guidelines recommend maintenance treatment for at least 1 year in patients who have had two depressive episodes or one severe episode, as well as in patients with chronic or recurrent depression (Birmaher et al., 2007). For patients with longstanding DD with superimposed MDD, lifetime maintenance should be considered (Birmaher et al., 2007). Other factors warranting maintenance treatment include comorbidity, severe functional impairment, marked suicidality, psychosis, family psychopathology, and significant psychosocial stressors (Birmaher et al., 2007).

PHARMACOLOGICAL TREATMENT FOR DEPRESSION IN CHILDREN AND ADOLESCENTS

In its nascent stages, child and adolescent psychiatry was forced to extrapolate from scientific data obtained from treatment research completed in the adult population. However, as the field advanced, it became clear that such extrapolations are not always correct or even safe. Tricyclic antidepressants (TCAs) are a good example, as their efficacy in adults has been proven consistently, yet they do not appear to be helpful in the treatment of depression in children, with only marginal evidence of efficacy in adolescents (Hazell & Mirzaie., 2013). There are currently only two antidepressants approved by the FDA for treatment of MDD in children and adolescents—fluoxetine for youths aged 8 to 18 years old and escitalopram for those aged 12 to 17 years old. Nevertheless, over the years there have been multiple antidepressant trials completed in the pediatric population, and the present literature will be reviewed to serve as a guide to evidence-based pharmacological treatment. These trials have been summarized in Table 12.1.

Selective Serotonin Reuptake Inhibitors

Fluoxetine

Fluoxetine is one of the best-known and most commonly prescribed antidepressants for adults. It was the first and remains the only selective serotonin reuptake inhibitor (SSRI) approved to treat depression in children as young as 8 years. The current recommended dosage range for children and adolescents with MDD is 10 to 20 mg daily, although dosages up to 40 mg were studied in one positive trial (March et al., 2004). The first double-blind placebo-controlled trial examining its effect in youths aged 13 to 18 years included only 40 participants, and it failed to show any statistical difference between the fluoxetine and placebo treatment groups (Simeon et al., 1990). The trial did include follow-up data after a mean interval of 24 months following study termination. Two thirds of participants and their parents from both the fluoxetine and placebo arms were interviewed to assess symptomatic improvement, but once again fluoxetine treatment failed to differentiate from placebo (Simeon et al., 1990). Two subsequent randomized controlled trials (RCTs) led to fluoxetine's FDA approval for depression in youths. Both studies looked at acute-phase treatment, with 96 patients randomized in the first study and 219 in the second (Emslie et al., 1997, 2002b). The first trial found clinically significant improvement with fluoxetine treatment

TABLE 12.1 Summary of Pharmacological Trials for Treatment of Depression in Children and Adolescents

Type of Pharmacological Treatment	*Citation*	*Design/Duration*	*Class Type*	*Sample Size (N)*	*Age Range*	*Results/Primary Outcome Measure*
Fluoxetine	Simeon et al., 1990	RCT 6 weeks	2	40	13–18	Fluoxetine = Placebo HAM-D
Fluoxetine	Emslie et al., 1997	RCT 8 weeks	1	96	7–17	Fluoxetine > Placebo CDRS-R, CGI ≤ 2
Fluoxetine	Waslick et al., 1999	Open label 8 weeks	3	19	8–18	↓ Symptoms of DD and MDD K-SADS, HAM-D, BDI, CGAS, CGI
Fluoxetine	Emslie et al., 2002	RCT 9 weeks	1	219	8–18	Fluoxetine > Placebo CDRS-R (≥30%)
Fluoxetine	March et al., 2004 (TADS)	RCT 12 weeks	1	439	12–17	Fluoxetine + CBT > Fluoxetine > CBT > Placebo ↓ CDRS-R, CGI-I
Fluoxetine	Emslie et al., 2004	RCT 32 weeks Maintenance	2	40	8–18	Fluoxetine > Placebo ↓ Relapse (CDRS-R > 40 w/2 week clinical deterioration)
Fluoxetine	Emslie et al., 2008	RCT 6 months Maintenance	1	102	7–18	Fluoxetine > Placebo ↓ Relapse (CDRS-R > 40 w/ & w/out 2 week clinical deterioration)
Escitalopram	Wagner et al., 2006	RCT 8 weeks	1	264	6–17	Escitalopram > Placebo for 12-17yo subpopulation ↓ CDRS-R
Escitalopram	Emslie et al., 2009	RCT 8 weeks	1	312	12–17	Escitalopram > Placebo ↓ CDRS-R
Sertraline	Wagner et al., 2003	RCT 10 weeks	1	376	6–17	Sertraline > Placebo ↓ CDRS-R
Sertraline	Rynn et al., 2006	Open label 24 weeks Maintenance	2	226	6–18	Sertraline = Placebo ↓ CDRS-R
Sertraline	Cheung et al., 2008	Open label 52 weeks Maintenance	3	22	13–19	Sertraline = Placebo HAM-D; recurrence/relapse determined clinically
Paroxetine, Imipramine	Keller et al., 2001	RCT 8 weeks	1	275	12–18	Paroxetine > Placebo HAM-D ≤ 8 or ↓ HAM-D ≥ 50%
Paroxetine, Clomipramine	Braconnier et al., 2003	RCT 8 weeks	1	125	12–20	Paroxetine = Clomipramine CGI, MADR-S
Paroxetine	Berard et al., 2006	RCT 12 weeks	1	286	13–18	Paroxetine = Placebo ↓ MADR-S ≥ 50%
Paroxetine	Emslie et al., 2006	RCT 8 weeks	1	206	7–17	Paroxetine = Placebo ↓ CDRS-R
Citalopram	Wagner et al., 2004	RCT 8 weeks	1	174	7–17	Citalopram > Placebo CDRS-R ≤ 28

(continued)

TABLE 12.1 (continued)

Type of Pharmacological Treatment	*Citation*	*Design/Duration*	*Class Type*	*Sample Size (N)*	*Age Range*	*Results/Primary Outcome Measure*
Citalopram	Shirazi et al., 2005	Open label 6 weeks	3	30	8–17	↓ HAM-D & CGAS > 50%
Citalopram	Von Knorring et al., 2006	RCT 12 weeks	1	244	13–18	Citalopram > Placebo w/ out psychotherapy K-SADS-P ≤ 2 (depr/anh) ↓ MADR-S ≥ 50%
Fluvoxamine	Sepehrmanesh et al., 2008	Open label 8 weeks	3	18	6–18	CDI, GAF and CGI-I
Venlafaxine	Mandoki et al., 1997	RCT 6 weeks	2	33	8–18	Venlafaxine = Placebo CDI, CBCL, HAM-D, CDRS
Venlafaxine ER	Emslie et al., 2007	RCT 8 weeks	1	367	7–17	Venlafaxine ER = Placebo ↓ CDRS-R
Duloxetine	Prakash, 2012	2 Open-label trials 8 weeks	3	776	7–17	Duloxetine > Placebo in trial II ↓ HAM-D
Duloxetine	Emslie et al., 2014	RCT 36 weeks	1	463	7–17	Duloxetine = Placebo ↓ CDRS-R
Duloxetine	Atkinson et al., 2014	RCT 36 weeks	1	337	7–17	Duloxetine = Placebo ↓ CDRS-R
Bupropion SR	Daviss et al., 2001	Open label 10 weeks	3	24	11–16	Clinician-rated ↓ in ADHD and depressive symptoms, along with child/parent/ teacher ratings
Bupropion SR	Glod et al., 2003	Open label 8 weeks	3	11	12–17	SIGH-SAD CGI-I
Nefazodone	Findling et al., 2000	Open label 6 weeks	2	28	7–17	↓ Depressive symptoms
Nefazodone	Rynn et al., 2002	RCT 8 weeks	1	195	7–17	Nefazodone = Placebo ↓ CDRS-R
Mirtazapine	Unpublished data, Organon Inc.	RCT 8 weeks	2	126	7–17	Mirtazapine = Placebo ↓ CDRS-R
Mirtazapine	Unpublished data, Organon Inc.	RCT 8 weeks	2	124	7–17	Mirtazapine = Placebo ↓ CDRS-R
Omega-3 FA	Nemets et al., 2006	RCT—pilot 16 weeks	2	28	6–12	Omega-3 FA > Placebo ↓ CDRS >50%

RCT = randomized controlled trial; HAM-D = Hamilton Depression Rating Scale; CDRS-R = Children's Depression Rating Scale, Revised; K-SADS-P = Kiddie-Schedule for Affective Disorders and Schizophrenia-resent episode version; BDI = Beck Depression Inventory; CGAS = Children's Global Assessment Scale; CGI = Clinical Global Impression; CGI-I = Clinical Global Impression-Improvement; TADS = Treatment of Adolescent Depression Study; MADR-S = Montgomery-Asberg Depression Rating Scale; GAF = Global Assessment of Functioning; CDI = Children's Depression Inventory ; CBCL = Child Behavior Checklist; ADHD = Attention Deficit Hyperactivity Disorder; SIGH-SAD = Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders.

based on CDRS-R and CGI measures, yet only 31% of fluoxetine participants attained remission as defined by a CDRS-R score of 28 or less compared to 23% of participants treated with placebo. Fluoxetine treatment was also superior to placebo in the second trial as measured by improvement in CDRS-R only, but remission rates for fluoxetine did separate from placebo with 41% versus 20% respectively. Emslie and colleagues (1998) also conducted a naturalistic follow-up of participants in their first fluoxetine study and found that approximately 40% of subjects had a recurrence of depression within 12 months, with 55% of those experiencing it within the first 6 months.

TADS ($N = 359$) randomized children aged 12 to 17 to receive fluoxetine treatment alone, CBT alone, or a combination of the two active treatments, versus placebo (March et al., 2004). In the fluoxetine-only arm, 60.6% were considered responders based on the primary outcome measures (CDRS-R total score and CGI-I improvement of "much" or "very much"). Although fluoxetine outperformed both placebo and CBT alone, the highest response rate obtained was 71.0% with the combination of fluoxetine and CBT. These findings first brought to light the benefits of combined treatment. TADS was the longest depression study in duration at 12 weeks. A treatment follow-up phase at 18 and 36 weeks showed continued improvement in all three arms of treatment (March et al., 2007). Fluoxetine treatment alone reached a response rate of 81% at week 36.

In terms of tolerability, commonly reported nonpsychiatric side effects in TADS included headache, gastrointestinal problems, sedation, and insomnia, thereby making fluoxetine quite easily tolerated by most children and adolescents. In regards to psychiatric side effects, fluoxetine treatment alone showed a statistically significant elevated risk of psychiatric adverse events, while the risk with combined fluoxetine and CBT treatment was intermediate between that of fluoxetine alone and CBT alone. Only two events—worsening depression with fluoxetine, and mania with placebo—met the adverse-event reporting criteria set forth by TADS, and all adverse events in the trial responded to treatment modification or discontinuation (March et al., 2004). Safety was specifically assessed for by looking at suicidality (Suicidal Ideation Questionnaire-Junior [SIQ-JR]) and harm-related adverse events. Although high-risk suicidality was an exclusion criterion, 29% of participants did report some suicidal ideation, which improved across all groups during the course of treatment. However, only the combination of CBT and fluoxetine proved to be statistically superior to placebo in decreasing suicidal ideation; fluoxetine alone did not. Seven participants did attempt suicide, but six of them already met SIQ-JR criteria for clinically significant suicidal ideation at baseline.

Currently, fluoxetine remains the oldest and most studied antidepressant to be approved for acute treatment of children and adolescents experiencing depression. It has reliable safety data and efficacy results supported by multiple type 1 and type 2 studies. In addition, two maintenance trials were conducted using fluoxetine. The first study ($N = 40$) showed fluoxetine to be superior to placebo in preventing relapse (defined as a CDRS-R score of more than 40 with 2-week clinical deterioration) when continued for 32 weeks following remission during acute treatment (Emslie et al., 2004). The second trial ($N = 102$), which followed youths for 6 months after initial response during open-label treatment, similarly demonstrated fluoxetine's superiority to placebo in preventing relapse and in increasing time to relapse in depressed youths (Emslie et al., 2008). Fluoxetine was also used in an open-label trial for treatment of dysthymic disorder, showing promise as an effective and safe treatment in the pediatric population (Waslick et al., 1999).

Escitalopram

Escitalopram is the second antidepressant approved for treatment of MDD in adolescents aged 12 to 17 years old. The usual dosage ranges from 10 to 20 mg/day. The first randomized placebo-controlled trial conducted with escitalopram in depressed children aged 6 to 17 years old ($N = 268$) showed no significant difference in improvement defined by the CDRS-R scores between the escitalopram group and the placebo group (Wagner et al., 2006). However, a post hoc analysis of the data showed a statistically significant difference across measures for the adolescent subpopulation aged 12 to 17 years old, as demonstrated by Clinical Global Impression–Severity (CGI-S), CGI-I, Children's Global Assessment Scale (CGAS), and CDRS-R scores at week 8. The second randomized placebo-controlled trial included 155 adolescents and found a statistically significant improvement in the escitalopram group compared to

the placebo group, with highest statistical difference at 4 weeks based on improvement in the CDRS-R score from baseline (primary outcome measure) (Emslie et al., 2009). Statistically significant improvement was also observable on CGI-I and CGI-S measures but not CGAS scores. Both studies were able to demonstrate statistical significance despite robust placebo responses (Emslie et al., 2009; Wagner et al., 2006), which had previously been noted in other pediatric antidepressant trials (Emslie et al., 2004; Wagner et al., 2004). Escitalopram was generally well tolerated in both trials, with side effects ranging from headache to influenza-like symptoms. Suicidality was not assessed systematically in the first study, but two suicide-related events were noted in the placebo group and one was noted in the escitalopram group. None of them was considered to be a serious adverse event (Wagner et al., 2006). In the second trial, suicidality was assessed using the clinician-rated Modified Columbia Suicide Severity Rating Scale (MC-SSRS) and the patient-rated SIQ-JR scale, while adverse events were categorized according to their relation to self-harm (Emslie et al., 2009). Both suicidal ideation and suicidal events were observed at a similar incidence in both the medication and placebo groups, with no indication of increased risk with medication treatment.

This second escitalopram trial did replicate the results obtained from post hoc analysis of the adolescent subpopulation in the first randomized placebo-controlled trial, which led to FDA approval. However, certain concerns with regards to generalizability remain, such as the lack of comorbid diagnoses in the trials, as well as the relative severity of depression of participants compared to those encountered in clinical practice. While FDA approved, escitalopram still lacks the strength of evidence that is available for fluoxetine.

Sertraline

Although not FDA approved for use in pediatric MDD, sertraline is FDA approved for obsessive-compulsive disorder (OCD) in children as young as 6 years. Typical pediatric dosage ranges from 25 to 200 mg/day. Three small open-label studies initially looked at sertraline treatment for adolescent MDD and showed promising results (Ambrosini et al., 1999; McConville et al., 1996; Nixon et al., 2001). These were followed by two multicenter randomized double-blind placebo-controlled trials that were conducted using sertraline in youths 6 to 17 years old (Wagner et al., 2003). Participants (N = 376) were assigned to 10 weeks of sertraline or placebo. Patients were selected to have at least a moderate severity of illness, but previous suicide attempters and high-risk subjects were excluded. Data from both trials were included in a prospectively defined combined analysis, with results at the primary endpoint showing statistically significant improvement in the sertraline arm when measured as improvement in CDRS-R scores. Secondary measures also showed statistical differences as early as 1 week into treatment. At study endpoint, 69% of sertraline patients met CDRS-R response criteria as opposed to 59% of placebo patients (Wagner et al., 2003). Sertraline was well tolerated overall despite a 9% discontinuation rate due to adverse events occurring mostly in children. Common side effects that were noted in at least 5% of sertraline participants and occurred twice as often when compared to placebo included agitation, diarrhea, anorexia, and vomiting. Suicide attempts occurred at the same rate in both medication and placebo groups (two in each arm), although the study was powered to look only at efficacy. Two subsequent open-label trials using sertraline for maintenance treatment have suggested some potential benefit, which merits further investigation (Cheung et al., 2008; Rynn et al., 2006).

Paroxetine

The usual adult dosage of paroxetine ranges up to 50 mg/day. Paroxetine is known to cause withdrawal upon abrupt discontinuation due to its short half-life, which can be quite a disadvantage in pediatric populations, where adherence can be inconsistent. Paroxetine has been investigated in three randomized placebo-controlled trials, only one of which yielded positive results (Berard et al., 2006; Emslie et al., 2006; Keller et al., 2001). The single positive study (Keller et al., 2001) looked at 275 youths who were assigned to an 8-week course of paroxetine, imipramine, or placebo in a 1:1:1 ratio. At endpoint, paroxetine did separate from placebo with statistical significance, with 63.3% of subjects attaining a HAM-D score of 8 or less (primary outcome measure) compared to 46% in the placebo group. These response rates rose to 76.1% and

57.6% respectively in patients who completed the full 8 weeks of treatment. Positive results were also observed in several secondary outcome measures. In terms of tolerance, common side effects were mostly benign, with only somnolence occurring at a significantly higher rate than in the placebo group. However, study withdrawal due to adverse events was the most common reason for discontinuation in the paroxetine group, with a rate of 9.7% compared to 6.9% in the placebo group. Suicidality was not assessed systematically, although psychiatric events were noted in the serious adverse event category. In the paroxetine group, there were two cases of worsening depression and five cases of "emotional lability" for which suicidal ideation or gestures were given as examples but without further details. There were two cases of conduct problems or hostility and one case of euphoria or expansive mood. These were ultimately not attributed to medication treatment. In the placebo group, one patient showed worsening of depression and another emotional lability. The latter was attributed to treatment with placebo, resulting in the patient's withdrawal from the study. Two subsequent randomized double-blind placebo controlled trials failed to show that paroxetine is more efficacious than placebo (Berard et al., 2006; Emslie et al., 2006). Another randomized trial comparing paroxetine to clomipramine showed no difference in efficacy between the two (Braconnier et al., 2003). Based upon these mixed and limited results from type 1 studies, paroxetine is generally not recommended for the treatment of pediatric depression.

Citalopram

The usual citalopram dosage in pediatric trials ranges from 10 to 40 mg/day, as the FDA has warned against doses exceeding 40 mg/day due to the risk of QT prolongation. There have been two randomized double-blind placebo-controlled trials (type 1 studies) looking at citalopram for treatment of pediatric MDD. The first trial followed 174 children aged 7 to 17 years; they were assigned to citalopram treatment or placebo for 8 weeks (Wagner et al., 2004). Compared to subjects taking placebo, those treated with citalopram showed a statistically significant improvement in CDRS-R scores as early as week 1, which persisted until endpoint. Additionally, 36% of patients in the citalopram arm met response criteria (CDRS-R score of 28 or less) compared to 24% in the placebo arm, a difference that also attained statistical significance. The most common adverse events were rhinitis, nausea, and abdominal pain in both the citalopram and placebo arms. Discontinuation rates due to adverse events were also very similar in both groups (5.6% for citalopram and 5.9% for placebo). Suicidality was not assessed systematically but none was reported, and the two cases of aggravated depression occurred in the placebo arm. Although a small citalopram pilot study assessing for efficacy and safety has shown a 16.7% switch to mania (Shirazi & Alaghband-Rad, 2005), no instance of conversion to mania was noted in this study. A second randomized placebo-controlled trial was conducted with citalopram in 244 adolescents aged 13 to 18 years over the course of 12 weeks (Von Knorring et al., 2006). Citalopram did not differentiate from placebo on either primary or secondary outcome measures. However, the study did allow for concurrent psychotherapy, which two thirds of participants were receiving. In patients who did not receive psychotherapy, citalopram treatment resulted in a higher response rate of 41% on the Schedule for Affective Disorders and Schizophrenia for school-aged children—Present episode version (Kiddie-SADS-P) compared to 25% for placebo. Citalopram also separated statistically from placebo in terms of improvement in Montgomery-Asberg Depression Rating Scale (MADR-S) scores. Response rates (defined as a 50% reduction in MADR-S score) in adolescents not receiving psychotherapy were 52% for citalopram and 45% for placebo, while remission rates were 22% and 19%, respectively. Most subjects tolerated the medication, with headache, nausea, and somnolence reported as the most common adverse side effects. Eighteen serious adverse events were reported with citalopram and 16 with placebo, with psychiatric hospitalization being the most common one. Fourteen patients in the medication arm reported treatment-emergent suicidality versus five patients in the placebo arm. However, a history of suicidality was common in this sample, with nearly one third of patients having previously attempted suicide.

Fluvoxamine

Although FDA approved for treatment of pediatric OCD for youth aged 9 years and up at a maximal dose

of 200 mg/day, fluvoxamine has not been the subject of any RCTs for treatment of depression in children or adolescents, and it is generally not used for such purposes. One open-label trial with 18 participants showed statistically significant improvement on CDI, Global Assessment of Functioning (GAF), and CGI-I measures, with no safety concerns (Sepehrmanesh et al., 2008).

Non–Selective Serotonin Reuptake Inhibitors

Venlafaxine (Extended-Release)

Typical adult dosages of venlafaxine range up to 225 mg/day. Dose-dependent increase in blood pressure warrants regular monitoring, and a shorter half-life puts patients at risk for discontinuation syndrome. The first study assessing the efficacy of venlafaxine in child and adolescent depression was a small randomized double-blind placebo-controlled trial, which recruited 40 youths between the ages of 8 and 18 years, assigning them to treatment with venlafaxine and psychotherapy versus placebo and psychotherapy (Mandoki et al., 1997). No difference was found between the two treatment arms. Two subsequent multicenter randomized trials (type 1 studies) were conducted with a total of 367 subjects aged 7 to 17 years receiving either venlafaxine extended-release (ER) (37.5 to 225 mg/day) or placebo. Initial results showed no statistically significant difference between the two treatment groups on any of the measures used. However, age-subgroup analysis demonstrated a significant difference in adolescents 12 to 17 years old, as shown by CDRS-R scores and several secondary outcome measures. CDRS-R responder rates in the adolescents were significant at 71% for venlafaxine ER, but the placebo response rate was considerable at 55%. Despite statistical significance, however, clinical significance was questionable in these trials due to the modest effect size of 0.28. Serious adverse events were reported at a rate of 7% (12 subjects) in the venlafaxine group versus 2% (3 subjects) in the placebo group; they included suicidal ideation, hostility, manic reaction, suicide attempt, overdose, agitation, and hallucinations, but no suicides (Emslie et al., 2007). These data were later included in the FDA meta-analysis of suicide-related events in pediatric patients from antidepressant treatment trials, demonstrating the highest risk estimates for suicide-related behaviors among the trials included (Hammad, 2004). Venlafaxine should therefore be used with caution and should be avoided as a first-line treatment for depression in the pediatric population as its risks may outweigh its questionable efficacy.

Duloxetine

The recommended adult dosage for duloxetine is usually 60 mg/day, with a maximal dosage of 120 mg/day. Three case reports have shown efficacious treatment with duloxetine in depressed female pediatric patients with comorbid pain (Desarkar et al., 2006; Meighen, 2007). One open-label study assessed the safety and pharmacokinetics of duloxetine in patients 7 to 17 years old with MDD (Prakash et al., 2012). It concluded that the medication is well tolerated and safe for use in children and adolescents, with dosing guidelines similar to adults. Two additional efficacy and safety studies of duloxetine in the treatment of childhood and adolescent depression were most recently published. They were both placebo-controlled but also used fluoxetine (20 to 40 mg/day) as an active control, and consisted of a 10-week acute-treatment phase followed by a 26-week extension-treatment phase. One of the studies used flexible dosing (60 to 120 mg/day) while the other used fixed dosing (30 mg or 60 mg), but both yielded inconclusive results as neither duloxetine nor the active control separated from placebo based on the mean change in total CDRS-R score (Atkinson et al., 2014; Emslie et al., 2014).

Bupropion

Bupropion is an antidepressant that is used in adults but is also prescribed off-label for attention-deficit/hyperactivity disorder (ADHD) in youths, with dosages ranging up to 450 mg/day administered in three divided doses. It is contraindicated in patients with eating disorders as it is more likely to cause seizures in this population. Once again, data are limited on the use of bupropion in depressed youths, with no double-blind RCTs available. One open study followed 24 adolescents (11 to 16 years old) with depression and comorbid ADHD during 8 weeks of treatment with bupropion flexibly titrated up to 3 mg/kg BID; it showed response rates of 88% for depressive symptoms, 63% for symptoms of ADHD, and

58% for both diagnoses (Daviss et al., 2001). Another open trial of 11 adolescents treated with 300 to 400 mg of bupropion sustained-release daily for 8 weeks showed a marked response with a significant decrease in scores on the Structured Interview Guide for the Hamilton Depression Rating Scale—Seasonal Affective Disorder Version (SIGH-SAD) (Glod et al., 2003).

Mirtazapine

The recommended mirtazapine dosage for adults is between 15 and 45 mg QHS, and its major side effects include sedation and weight gain. Two unpublished multicenter randomized placebo-controlled trials were conducted using mirtazapine in depressed youths, with a total of 259 subjects aged 7 to 17 years (unpublished data on file with Organon Inc., Cheung et al., 2006). There was no statistical difference between the mirtazapine and placebo arms in CDRS-R total scores in either study.

Nefazodone

Nefazodone is notable for causing hepatotoxicity that can be fatal or so severe as to require a liver transplant. It has been taken off the market is some countries such as Sweden, but it remains available in the United States with the addition of a black box warning. The FDA currently estimates that about one case of liver failure is reported per 250,000 to 300,000 patients who have taken the medication for at least a year. Typical adult dosing for depression is 150 mg to 300 mg BID. An open-label trial was initially conducted with nefazodone, evaluating pharmacokinetics in 28 depressed youths ages 7 to 17 years (Findling et al., 2000). Results showed reduction in depressive symptoms after 6 weeks of treatment. A double-blind randomized placebo-controlled trial followed, looking at 195 adolescents treated with 300 to 400 mg of nefazodone daily for 8 weeks, but it did not show a statistical difference between the two groups on the primary outcome measure, the CDRS-R score (Emslie et al., 2002a). It did, however, show statistical significance on the secondary outcome measure, the HAM-D score. To be noted, the study also mentioned a second unpublished trial showing no significant distinction between nefazodone treatment and placebo in a depressed pediatric population.

Tricyclic Antidepressants and Monoamine Oxidase Inhibitors

Although quite efficacious in adults, TCAs have been consistently shown to be ineffective for depressed children, with only marginal evidence for possible use in adolescents (Hazell et al., 1995, 2002). Their lack of efficacy and adverse side-effect profile, as well as potential lethality in overdose, do not make this class of medications a treatment option for pediatric depression. Monoamine oxidase inhibitors (MAOIs) have not been investigated significantly in youths and carry the particular disadvantage of requiring a tyramine-free diet. The selegiline patch differs from other MAOIs by its selectivity for MAO B, as it bypasses hepatic first-pass metabolism and avoids inhibition of MAO A in the liver and gastrointestinal tract (Lee & Chen, 2007). As a result, it does not require any dietary restrictions in doses up to 6 mg/24 hours, and it has recently been evaluated in a double-blind placebo-controlled trial in youths. It was determined to be safe and well tolerated, but a paper presented at the 2011 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP) did not show any statistical difference in terms of improvement of depressive symptoms in adolescents treated with the selegiline transdermal system compared to placebo (DelBello et al., 2011).

Omega-3 Fatty Acids

Used widely as supplements to improve cardiovascular health, and believed to reduce nonspecific inflammation, omega-3 fatty acids have also been investigated in the treatment of adult depression and other psychiatric disorders. Studies in children include treatment for ADHD, bipolar disorder, and autism. One open pilot study looking at 28 children aged 6 to 12 years showed significant improvement in depressive symptoms with omega-3 fatty acids in comparison to placebo (Nemets et al., 2006).

COMORBIDITY

Psychiatric comorbidity is quite common, with 40% to 90% of depressed youths carrying a comorbid diagnosis, most frequently an anxiety disorder, ADHD, or substance abuse disorder (Birmaher et al., 2007; Lewinsohn et al., 1998, 2003). Comorbidity of MDD

with dysthymia has shown the highest correlation with a poor prognosis as well as poor response to treatment with SSRIs (Emslie et al., 1998; Kratochvil et al., 2009). Comorbid ADHD has been associated with moderation of treatment response in TADS (Curry et al., 2006), as well as lower response rates to treatment with paroxetine, imipramine, and even placebo (Birmaher et al., 2000). Response rates among patients without ADHD were 71% for paroxetine, 64% for imipramine, and 59% for placebo, whereas rates for patients with ADHD were 25% for paroxetine, 31% for imipramine, and 13% for placebo (Keller et al., 2001). Substance use disorders tend to be more common in adolescents with treatment-resistant depression, predicting poor treatment response in the TORDIA study (Emslie et al., 2010). There have been very few trials looking at the optimal sequence of treatment in patients with psychiatric comorbidities, which leaves clinicians with little to no guidance (Hughes et al., 2007; Rey & Birmaher, 2009). Nevertheless, usual practice involves determining which disorder is causing the most distress and the greatest impairment in functioning, and treating it first (Birmaher et al., 2007). One must also keep in mind that the treatment of one co-occurring psychiatric condition can also be useful in treating the other. In the case of comorbid depressive and substance abuse disorders, both conditions need to be treated simultaneously as they worsen each other's prognosis, and their co-occurrence itself has been shown to be a risk factor for completed suicide (Goldstein, 2009).

TREATMENT-RESISTANT DEPRESSION

Before proceeding with the management for treatment-resistant depression, it is important to establish nonresponse and address any underlying factors that may be contributing to failure of treatment. Most commonly, such factors include nonadherence to treatment, inaccurate diagnosis, untreated comorbidity (psychiatric and/or medical), insufficient length of treatment, and inadequate medication dosage (Birmaher et al., 2007). The initial management strategy consists of optimizing a patient's ongoing treatment in terms of dosage and duration (Birmaher et al., 2007; Hughes et al., 2007). However, if the child or adolescent is showing no response at all or is experiencing intolerable side effects with the current antidepressant, a different antidepressant should be tried. The TORDIA study is the only RCT looking at pharmacological strategies in SSRI-resistant adolescent depression (Brent et al., 2008). Three hundred thirty-four participants (aged 12 to 18 years) with MDD who had not responded to one adequate SSRI trial were randomized to one of four treatment options for 12 weeks: switch to another SSRI (fluoxetine, paroxetine, or citalopram) with or without CBT, or switch to venlafaxine with or without CBT. Results showed that patients who were switched to another antidepressant showed a 40.5% response rate, regardless of the antidepressant class. Medication monotherapy, however, was inferior to switching to a different antidepressant with the addition of CBT, which led to a response rate of 54.8%. Although venlafaxine appeared to be as efficacious as the alternate SSRIs, it was less well tolerated. Another strategy for management of treatment-resistant depression is augmentation, which is usually considered when a partial response is already being observed. A post hoc analysis of the TORDIA study demonstrated higher remission rates with the addition of a mood stabilizer (atypical antipsychotic, lithium, divalproex, or topiramate) to an SSRI (Emslie et al., 2010). Fifty percent of those patients showed remission compared to 17% for patients who did not receive a mood stabilizer. Recommendations for augmentation strategies as well as class switching generally follow adult evidence, as very few data are available for use in children and adolescents (Hughes et al., 2007; Rey & Birmaher, 2009).

SUICIDALITY AND THE BLACK BOX WARNING

In October 2004, the FDA issued a black box warning for all antidepressants, addressing concerns of increased suicidal thinking and behavior in children and adolescents in the acute phase of antidepressant treatment. A meta-analysis was conducted with data from 24 trials for a pooled total of 4,582 subjects (Hammad et al., 2006). There were 16 studies looking at MDD, 4 at OCD, 2 at GAD, 1 at ADHD, and one at social anxiety. Results indicated an overall risk ratio of 1.95 for all antidepressants across indications and a lower risk of 1.66 for SSRIs in depression trials. A second meta-analysis (Bridge et al., 2007), which included three additional trials (both published and unpublished), showed a pooled absolute rate of 3%

for suicidal ideation or suicide attempt in patients with MDD treated with antidepressants, compared to 2% for patients with the same diagnosis and treated with placebo. As depression itself may lead to suicidal ideation and suicide attempts, it is important to weigh the risk of treatment with the actual risk of suicide—occurring most often in youths with unipolar or bipolar depression (Bridge et al., 2006)—and proceed with frequent symptom-specific monitoring. Moreover, a study by Lu and colleagues (2014) has been interpreted as indicating that the warning about the emergence of suicidal ideation in patients taking antidepressant medication may have had the paradoxical effect of increasing the rate of suicide attempts. They reported that the safety warnings, which received widespread media coverage, were associated with both a reduction in the rate of antidepressant prescribing and an increase in suicide attempts in young adults.

ACTIVATION AND CONVERSION TO MANIA

Activation, which consists of increased activity, irritability, insomnia, and disinhibition presenting in the first few weeks of treatment (Goodman et al., 2007; Safer & Zito, 2006), is thought to occur more commonly in children than in adolescents and adults (Safer, 2011) and has also been suggested as a precursor to antidepressant-related suicidality (Goodman et al., 2007). It is therefore recommended to start antidepressants in children at a low dose, titrating upward slowly and cautiously. Conversion to mania as a result of antidepressant treatment is also of significant concern, although rates have been low across RCTs conducted in youths. Patients should be assessed for risk factors for BD such as family history of BD, very-early-onset depression, psychosis, or previous manic switch, and should be monitored accordingly (Choe et al., 2012).

PSYCHOSOCIAL TREATMENTS FOR DEPRESSION IN CHILDREN AND ADOLESCENTS

Due to the high prevalence and chronicity of pediatric depression if left untreated, it is important to understand the available and effective psychosocial treatments in addition to the pharmacological options (Lewinsohn & Clarke, 1999; Weersing & Brent, 2006). Far too often, depressed youth do not receive effective treatment despite its availability (Lewinsohn & Clarke, 1999), which in turn can lead to long-term functional and social impairment (Mufson et al., 2004b). The psychosocial treatments for pediatric depression with the largest evidence base include CBT and IPT-A (Stark et al., 2012). Additionally, recently developed approaches are showing encouraging treatment gains in preliminary research. Such interventions include Attachment-Based Family Therapy (ABFT) and Parent–Child Interaction Therapy (PCIT) for younger pediatric populations, and some support is emerging for psychodynamic therapies (Diamond et al., 2002; Luby et al., 2012; Trowell et al., 2007).

To provide a comprehensive yet content-specific review, we only include and examine studies that used an RCT design with the primary purpose of reducing depressive symptoms. For example, this review excludes prevention studies that targeted youth who were not presenting with depressive symptoms. Although the results of other studies warrant consideration for the potential to reduce rates of afflicted children and adolescents, such a discussion is beyond the scope of the present chapter.

Cognitive-Behavioral Therapy

CBT has been extensively researched as a psychosocial intervention of choice for depression in children and adolescents, with RCTs that offer promising outcomes (Compton et al., 2004). These studies demonstrated that CBT may be more effective than other psychosocial interventions such as family therapy, supportive counseling, and relaxation training (Brent et al., 1997; Wood et al., 1996). Traditional CBT for depression uses skills training toward recognizing and restructuring negative patterns of thought that will ultimately stimulate changes in behaviors (Beck, 2011; Kaslow & Thompson, 1998). Often, CBT for children and adolescents incorporates additional sessions to include parents and other family members to support the child and his or her treatment (Compton et al., 2004). Other basic techniques used in these interventions include (TADS Team, 2000):

1. Mood monitoring
2. Cognitive restructuring

3. Behavioral activation, pleasant activity scheduling, and goal-setting strategies
4. Relaxation and stress management
5. Social skills and conflict-resolution training
6. Training in general problem-solving skills

Numerous research studies involving RCTs have evaluated the effectiveness and efficacy of individual CBT for depressed children and adolescents. These studies, and meta-analyses of these studies, suggest that CBT offers significant symptom improvement and treatment gains compared to waitlist conditions and treatment-as-usual groups (Compton et al., 2004; Klein et al., 2007). In a type 2 RCT, 53 adolescents with MDD received five to eight sessions of individual CBT treatment or relaxation training, Wood and colleagues concluded that CBT resulted in significantly greater improvement on various measures of mood, depressive symptoms, and overall functioning (Wood et al., 1996). In another type 2 RCT, Brent and colleagues (1997) randomized 107 adolescents with MDD to receive 12 to 16 sessions of individual CBT, family therapy, or supportive therapy. Findings indicated that adolescents in the CBT treatment arm had lower rates of depression diagnoses at the end of treatment. In both these studies, individual CBT was superior to other interventions at the end of treatment; however, these differences between groups did not persist at the 6-month (Wood et al., 1996) and 2-year follow-up assessments (Brent et al., 1997) respectively.

The efficacy of group CBT has also been well established in the treatment of depression in children and adolescents (David-Ferdon & Kaslow, 2008). Clarke and colleagues (1999) conducted a type 1 RCT in which 123 adolescents with MDD or dysthymia were randomly assigned to 8 weeks of group CBT, group CBT with a separate parent group, or waitlist control. Patients in both the group CBT treatment arms had higher depression recovery rates (64.9% and 68.8%) compared to those in the waitlist control group (48.1%). Outcomes in the two CBT treatment arms did not significantly differ from each other. For children, group CBT is currently the most efficacious psychosocial intervention to treat depression, with support from multiple type 2 studies (Asarnow et al., 2002; Stark et al., 1987, 1991). More generally, reviews of rigorous treatment outcome studies conclude that adolescent-only group CBT, child-only group CBT, and child group CBT plus a parent component have sufficient empirical support for the treatment of depression, with stronger support than that of CBT delivered individually (David-Ferdon & Kaslow, 2008).

An emerging area of research supports the use of computerized versions of CBT for depressed children and adolescents (Richardson et al., 2010). The findings of two type 2 RCTs, one with male participants and one with females, suggest that computerized CBT interventions situated as part of high-school curriculums offer some benefits in reducing depressive symptoms (O'Kearney et al., 2006, 2009). The participants in these studies presented with depressive symptoms but did not meet criteria for a depressive disorder. In the first of those studies, 78 male adolescents with depressive symptoms were randomized to the Internet-based CBT program (five modules) or a usual curriculum of developmental activities (O'Kearney et al., 2006). At the end of the treatment period, adolescents who had completed three or more modules of the CBT program had improvements in depressive symptoms, attributional patterns, and self-esteem, but only the effect for self-esteem was sustained at 16 weeks after treatment (O'Kearney et al., 2006). The same Internet program, employed with adolescent females, demonstrated more rapid improvements of depressive symptoms in the group receiving the CBT Internet program, with effect sizes of these differences reaching statistical significance from the posttreatment point to 20 weeks after that (O'Kearney et al., 2009). Both studies found that completion rates of the Internet program were problematic, with the most depressed individuals tending to complete fewer modules (O'Kearney et al., 2009), suggesting the need for additional treatment development.

More recently, a pilot double-blind type 2 RCT compared another self-help computerized CBT program called "The Journey" (cCBT) with a control attention placebo program with brief psychoeducational content (CPE) among 34 adolescents (aged 13 to 18 years) in a school setting (Stasiak et al., 2014). Participants were referred by school counselors and were eligible to participate if they scored 30 or more on the CDRS-R or 76 or more on RADS-2, indicating a possible depressive disorder or risk for major depressive symptoms, respectively. Unlike the two previous studies, completion rates were much higher at 94%, with 89% of them liking the program enough to recommend it to others, indicating both feasibility and acceptability of cCBT in this setting. This increase

in completion rates over previous studies (O'Kearney et al., 2006, 2009) is hypothesized to be due to the perceived attractiveness of cCBT's interface, ease of use, and appropriate language and difficulty level to meet adolescents' needs. Additionally, preliminary efficacy was shown by significantly greater improvement in CDRS-R scores and problem-solving skills for adolescents treated with cCBT compared to the CPE program (Stasiak et al., 2014).

Until recently, most of the research that supported the efficacy of CBT to treat pediatric depression compared CBT to other psychosocial interventions, waitlist controls, or treatment as usual. Very few pediatric depression studies have looked at combination treatments of CBT and medication or compared them to each other. As discussed earlier in this chapter, TADS is one of the most compelling type 1 studies to document the efficacy of combined CBT and fluoxetine treatment as superior to CBT alone, fluoxetine alone, and placebo for adolescents with MDD. Adolescents assigned to the treatment arms that offered CBT in this study received 15 50- to 60-minute sessions over 12 weeks. These sessions involved the techniques mentioned earlier and integrated parent and family sessions as needed. CBT significantly enhanced treatment with fluoxetine, leading to the highest response rate of 71.0% among all treatments (March et al., 2004). The combination of CBT and fluoxetine was also superior to CBT alone and placebo with respect to probability of remission, quality of life, and multiple measures of acceptability, tolerability, and safety. Patients receiving fluoxetine alone were twice as likely as those receiving the combination treatment to experience a suicidal event, suggesting that CBT may have had a protective effect against suicidality among patients receiving combination treatment. Findings from the longitudinal analyses of TADS suggest that the long-term response rates (at weeks 18 and 36) for treatment with CBT alone are comparable to those for combined treatment and treatment with fluoxetine alone (TADS Team, 2007). Another type 1 study that demonstrated the increased efficacy of combined treatment was the TORDIA RCT, where adolescents with MDD who had failed to respond to an adequate SSRI trial were randomized to switch to another medication with or without CBT for 12 weeks. Results indicated that switching to a combination of CBT with another medication led to significantly higher response rates than switching to another medication without CBT (54.8%; Brent et al., 2008). This study highlighted combination treatment as an effective intervention for adolescents with chronic treatment-resistant depression.

In various studies examining CBT, research suggests that certain cognitive styles are associated with better treatment outcomes. Adolescents and children with lower levels of hopelessness, less negative thinking, and fewer distortions in their thought processes generally experience greater improvement with treatment (Becker et al., 2008). Additionally, individuals at higher levels of functioning and those who were diagnosed with depression at younger ages tended to evidence greater improvements after individual CBT treatment (Jayson et al., 1998).

Interpersonal Psychotherapy for Adolescents

IPT-A is a brief, structured, manualized intervention targeting specific relational problem areas to reduce depressive symptoms and improve social functioning (Moreau et al., 1991; Mufson et al., 2004b). The problem areas or developmental issues addressed over the course of treatment include grief, role disputes, role transitions, and interpersonal deficits (Mufson et al., 2004b). Through IPT-A, the youth learns strategies to cope with these challenges, especially in regard to overcoming interpersonal obstacles with friends and family members (Mufson et al., 2004b). IPT-A was adapted by Moreau and colleagues (1991) from the original IPT manual designed for depressed adults (Klerman et al., 1984). It typically consists of 12 individual sessions, 30 to 60 minutes each, conducted over a 12- to 16-week period. The techniques most commonly used include psychoeducation, communication analysis, encouragement of affect expression, role playing, and interpersonal problem solving (Moreau et al., 1991). IPT-A has been modified for use with depressed adolescents in the following ways: shorter treatment duration, parental involvement, and a more narrowly defined assignment of the "sick role" (e.g., helping the adolescent to understand his or her depression as an illness rather than a personal shortcoming) in order to encourage the patient to participate in activities as normally as possible (Brunstein-Klomek et al., 2007).

There have been a number of research studies evaluating the efficacy of IPT-A to treat adolescent depression. Through RCTs, situated within hospital and school-based clinics, researchers found that

IPT-A reduced depressive symptoms and improved global and social functioning in depressed adolescents (Mufson et al., 1999, 2004a, 2004c; Rosselló & Bernal, 1999). One of the first type 1 RCTs of IPT-A compared the 12-week intervention to routine clinical monitoring, consisting of monthly or biweekly supportive therapy, for 48 participants with MDD referred to a hospital clinic (Mufson et al., 1999). After treatment, significantly more adolescents in the IPT-A group (75%) met depression recovery criteria on the HAM-D than control patients (46%). IPT-A participants also reported greater improvement in overall social functioning in friendships, dating relationships and interpersonal problem solving. In a subsequent type 2 RCT within school-based clinics, 63 adolescents who met criteria for a depressive disorder were randomized to receive 16 weeks of IPT-A or treatment as usual, which most closely resembled supportive counseling (Mufson et al., 2004c). Treatment outcomes were similar to those of the initial hospital clinic trial: Adolescents in the IPT-A group showed improvements in self-reported and clinician-reported depressive symptoms and overall social and psychological functioning. This study was one of the first to assess the effectiveness of delivering an evidence-based intervention for depressed adolescents by school-based clinicians in a community setting (Mufson et al., 2004c). In both these studies, the samples were predominantly female and Hispanic and of low socioeconomic status, limiting generalizability to other adolescent populations.

In 2004, Mufson and colleagues adapted individual IPT-A to be delivered in a group format (IPT-AG). This format provides an immediate forum for adolescents to be able to practice new interpersonal interactions and is also more cost-effective and feasible for implementation in school-based clinics and other community mental health settings. Data from type 2 and type 3 studies suggest IPT-AG's feasibility, acceptability, and preliminary benefits in reducing depression symptoms (Mufson, 2004, Mufson et al., 2004d; Rosselló et al., 2008), with further research under way.

As expected, interpersonal functioning has been indicated as a moderator of treatment outcome among adolescents. In particular, conflict in patients' relationships with their mothers and friends prior to receiving treatment predicted greater symptom relief for adolescents receiving IPT-A compared to those in the control condition, although problems in family functioning also slowed the pace of those symptom improvements (Gunlicks-Stoessel et al., 2010). The authors also found that less favorable treatment outcomes were predicted by adolescents' perception of their own dysfunction (Gunlicks-Stoessel et al., 2010). The increased age of patients, greater severity of depression, presence of comorbid disorders, and elevated levels of cortisol during interpersonal conflict tasks have also been shown to moderate the effects of treatment using IPT-A (Gunlicks-Stoessel et al., 2013; Mufson et al., 2004b; Young et al., 2006).

Other Psychotherapy Approaches

Attachment-Based Family Therapy

Based on structural and multidimensional family therapy, ABFT is a manualized treatment drawing from contextual therapy, emotion-focused therapy, and attachment theory (Diamond et al., 2002). Developers of ABFT suggest that a family-based treatment is particularly important for children and adolescents as factors within parent–child relationships are related to an individual's development of depression and maintenance of symptoms (Diamond et al., 2002). Stemming from this assertion, ABFT is based on the assumption that poor attachment, high conflict, and criticism in parent–child relationships can result in serious negative consequences when combined with inadequate affective attunement (Diamond et al., 2002). Additionally, ABFT came about as a result of the expectation that these problematic attachments can be improved as parents learn how to be better caregivers and adolescents rebuild better trust and communication. Resulting gains in these areas of functioning reduce adolescents' symptoms of depression while preventing possible relapse (Diamond et al., 2002).

ABFT is organized around five treatment tasks:

1. *Rational Reframe Task*: Refocuses the intervention on improving relationships within the family rather than "fixing" the patient and assigning blame
2. *Adolescent Alliance-Building Task*: Emphasizes the importance of building a therapist–adolescent bond and identifying specific and stressful intrafamily conflicts for eventual discussion with parents

3. *Parent Alliance-Building Task*: Encourages parents to examine their personal stressors and explore their own attachment experiences
4. *Attachment Task*: Adolescent communicates with parents about previously concealed emotions and conflicts in the parent–child relationship.
5. *Competence-Promoting Task*: Parents focus on supporting the adolescent's success in relationships and connections outside the family as conflict decreases within.

In a type 2 study conducted in 2002, Diamond and colleagues compared treatment outcomes of adolescents with MDD receiving ABFT to a waitlist control group. Researchers found that participants treated with ABFT for 12 weeks demonstrated greater reductions in depression diagnoses and severity of depressive symptoms, including hopelessness and suicidality, along with improvements in attachment relationships with mothers (Diamond et al., 2002). Recent research also indicates that ABFT offered relief from depressive symptoms more rapidly than enhanced usual care in a small type 2 RCT for adolescents with suicidal ideation (Diamond et al., 2010).

Psychodynamic and Supportive Therapies

Traditionally, there have been fewer research studies suggesting empirical support of psychodynamic therapies to treat childhood and adolescent depression (Trowell et al., 2007). Recently, however, researchers at three international sites conducted a type 2 RCT, assigning 72 children (aged 9 to 15) diagnosed with MDD to receive short-term individual psychodynamic therapy focused on interpersonal relationships and attachments or family therapy (Trowell et al., 2007). Analysis at the end of treatment and at follow-up indicated that there were no significant differences between the two treatment groups but that the majority of participants evidenced improvement in symptoms and functioning (Trowell et al., 2007).

Parent-Child Interaction Therapy Emotional Development

No treatments have been empirically validated for use with depressed children between the ages of 3 and 6 years. Therefore, Lenze and colleagues (2011) created an Emotional Development (ED) module, which was integrated into PCIT, to adapt the treatment for use with depressed children. In its original format, PCIT is primarily used for families with a child displaying oppositional defiant and disruptive behaviors and involves real-time parent coaching during interactions with the child (McNeil & Hembree-Kigin, 2010). The additional ED module addresses emotion development impairments identified in preschool-onset depression. Luby and colleagues (2012) further investigated the efficacy and feasibility of PCIT-ED in a type 2 pilot RCT comparing the treatment to psychoeducation. The findings suggest that PCIT-ED significantly improved executive functioning and increased recognition of emotion, although there were no differences between the treatment conditions on depressive symptoms or functional impairment (Luby et al., 2012).

CONCLUSION AND FUTURE DIRECTIONS

Depression is a common and impairing condition that accounts for a substantial proportion of disability and mortality among children and adolescents. This chapter reviews the evidence base for pharmacological and psychosocial interventions to treat pediatric depression. Multiple type 1 and type 2 RCTs have demonstrated the efficacy of the following treatments. The two antidepressant medications that are FDA approved for treatment of MDD in children and adolescents are fluoxetine (for patients aged 8 to 18 years) and escitalopram (for patients aged 12 to 17 years), and both are well tolerated among pediatric patients (Birmaher et al., 2007; Emslie et al., 2002, 2009; TADS, 2004). Fluoxetine remains the oldest and most studied antidepressant to be approved for acute treatment of pediatric depression. Two psychosocial interventions have been shown to be the most efficacious for treating pediatric depression: CBT and IPT-A. CBT has demonstrated efficacy as an individual treatment for adolescents (Brent et al., 1997; Compton et al., 2004; TADS, 2004; Wood et al., 1996) and as a group treatment for both children and adolescents with depression (Asarnow et al., 2002; David-Ferdon & Kaslow, 2008; Clarke et al., 1999; Stark et al., 1987, 1991). IPT-A has demonstrated efficacy as an individual treatment for adolescents with depression (Mufson et al., 1999, 2004b).

TADS was a pivotal type 1 study that established the efficacy of combined treatment with CBT and fluoxetine as superior to either treatment alone for adolescents with MDD (March et al., 2004). The TORDIA RCT further established that adolescents with chronic, treatment-resistant depression were more likely to respond to a combination treatment of CBT and a switch in antidepressant medication than to a switch in medication alone (Brent et al., 2008). Overall, psychosocial interventions are recommended as first-line treatments for adolescents with brief or mild depression. In children and adolescents with moderate to severe depression, treatment with medication alone or in combination with CBT is most effective. Adding CBT to medication may enhance the safety of medication (TADS Team, 2007).

Despite a significant number of RCTs (type 1 and 2 studies) carried out thus far, evidence-based pharmacological recommendations remain limited in the treatment of depressive disorders in children and adolescents. Medications that have consistently shown response in adults have not demonstrated similar efficacy in youths (Ryan, 2003), and adverse effects have proved to be more concerning in the pediatric population (Bridge et al., 2007). It has therefore become quite clear that treating depression in children and adolescents is not merely an extension of adult protocols. Very few medications are currently FDA approved, leaving physicians with narrow treatment strategies and families with few pharmacological options to choose from. As SSRI trials continue to show inconsistent results, non-SSRIs should be investigated further, most importantly in studies sufficiently powered to determine efficacy and safety. Long-term maintenance and prevention studies, also assessing long-term safety, are also crucial to forge ahead with a comprehensive long-term treatment/prevention model. Factors currently known to affect treatment response include severity of illness, age of onset, duration, comorbidity, family history, and environmental stressors. However, more specific predictors of response and remission should be explored in pharmacological studies in order to directly improve prognosis. Biological markers also warrant further investigation to help elucidate vulnerability as well as guide treatment beyond a simple trial-and-error model.

The aforementioned benefits of psychosocial treatments for childhood and adolescent depression suggest that these interventions remain an important and viable option as alternatives and/or additions to medication treatment. With empirically supported versions of new and more traditional interventions emerging and generating promising research, psychotherapy continues to merit consideration to help children and adolescents with depression. Future research should continue to investigate the implications of the consistent observation that the differential response rates between evidence-based treatments and their control counterparts fail to maintain statistical significance beyond the end of treatment. To this end, analysis of the functional components offering the greatest symptom alleviation for depressed pediatric populations appears to be a worthy examination.

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13

Psychosocial Treatments for Major Depressive Disorder

W. Edward Craighead
Benjamin N. Johnson
Sean Carey
Boadie W. Dunlop

Behavior therapy (BT), cognitive-behavior therapy (CBT), and interpersonal psychotherapy (IPT) have each been shown by at least two type 1 or type 2 randomized controlled trials (RCTs), as well as by numerous meta-analytic reports of the literature, to be effective psychosocial interventions for patients meeting criteria for major depressive disorder (MDD). All three psychosocial treatments have yielded substantial reductions in scores on the two major depression rating scales (the Beck Depression Inventory [BDI] and the Hamilton Rating Scale for Depression [HRSD]), significant decreases in the percentage of patients meeting the criteria for MDD at the end of treatment, and substantial maintenance of effects well after treatment has ended. The data for outcomes of psychosocial and pharmacological interventions for MDD episodes suggest that the two treatment modes are equally efficacious. Meta-analyses lend support for the superior effectiveness of combined psychosocial and pharmacological treatments with chronic depression. Recently published data suggest that psychosocial interventions may also be as effective as antidepressant medications for some patients with more severe forms of depression. Current research efforts are examining methods to better match individuals to the specific form of treatment most likely to prove beneficial.

INTRODUCTION

MDD is one of the most commonly diagnosed psychiatric disorders among adults, with U.S. lifetime prevalence rates of approximately 17%, with rates of 20% to 25% for women and 9% to 12% for men; point prevalence rates are approximately 6% and 3% for women and men, respectively (Ferrari et al., 2013; Kessler et al., 2005).

Prevalence rates and gender differences are relatively constant across the adult lifespan. In addition, the diagnosis of MDD has increased over the past 30 years (Fergusson, Horwood, Ridder, & Beautrais, 2005; Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993; Weissman et al., 1996); this suggests that the lifetime prevalence will be higher for current younger cohorts (for an alternative view, see Baxter et al., 2014). The age of first episode of MDD has been decreasing (Burke, Burke, Regier, & Rae, 1990; Lewinsohn, Clarke, Seeley, & Rohde, 1994), so that the peak years for first onset are at present between 15 and 29 years of age (Burke et al., 1990; Fergusson et al., 2005; Hankin et al., 1998). The earlier onset of a first depressive episode has been linked to more

chronic MDD (Mondimore et al., 2007). Regardless of age of onset, 75% of patients with MDD will experience multiple depressive episodes (Hughes & Cohen, 2009). Thus, MDD is a major health problem for which it is important to have efficacious treatments and ultimately to personalize treatment by matching interventions to empirically derived subtypes of depression.

Depression engenders not only extraordinary personal and family suffering but also significant societal burdens, such as role impairment and an increased use of social and medical services (Johnson, Weissman, & Klerman, 1992; Merikangas et al., 2007). Furthermore, there are enormous financial costs for treatment and for lost productivity due to absenteeism from work (Greenberg, Stiglin, Finkelstein, & Berndt, 1993; Wells et al., 1989). MDD costs an estimated $36 billion each year in the United States, including an annual $11.7 billion in lost productivity (Kessler et al., 2006). MDD is among the top three major causes of societal and economic disease burden across the globe (Ferrari et al., 2013; Mathers & Loncar, 2006; World Health Organization, 2008). The sequelae following the first episode of MDD are substantial. The probability of subsequent episodes is significantly increased, so that most now consider MDD a recurrent or chronic disease. For example, a recent study found that approximately 73% of teens who experienced a first episode before age 18 had a recurrence within the next 12 years (Pettit, Hartley, Lewinsohn, Seeley, & Klein, 2013).

To receive a diagnosis of MDD a person must experience marked distress or a decrease in level of functioning. In addition, the 2 weeks before examination must be characterized by the almost daily occurrence of a dysphoric mood (sad, empty, or hopeless) or a loss of interest or pleasure in almost all activities (American Psychiatric Association [APA], 2013). The individual must also experience at least four (only three if both dysphoric mood and anhedonia are present) of the following seven symptoms (with the second through sixth occurring nearly every day):

1. Significant weight loss (while not trying to lose weight), significant weight gain, or a change in appetite
2. Insomnia or hypersomnia
3. Psychomotor agitation or retardation
4. Fatigue or loss of energy
5. Feelings of worthlessness or excessive or inappropriate guilt
6. Decreased concentration or indecisiveness
7. Recurrent thoughts of death or suicidal ideation, plan, or attempt

Substantial advances have been made over the past three decades in the treatment of depression. Treatments of choice now include a number of psychosocial interventions—BT (including behavioral marital therapy [BMT]), CBT, and IPT—in addition to the somatic interventions reviewed in a separate chapter. This chapter reviews the evidence regarding the efficacy of these specific psychosocial treatments (including their combinations with somatic treatments), discusses the possible mechanisms of change in these therapies, and addresses issues regarding the appropriate use of psychosocial treatments. This review includes only those studies that obtained information for diagnosis via a structured interview such as the Structured Clinical Interview for *DSM* (SCID; First, Spitzer, Gibbon, & Williams, 1995; Spitzer, Williams, Gibbon, & First, 1992) and employed a formal, defined diagnostic system such as the Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978) or the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (*DSM*-5; APA, 2013). Further, to be included, an investigation must also have employed cutoff scores on standard depression severity measures, such as clinical rating scales or self-report measures, as a criterion for admission to the study. Thus, by virtue of the severity, frequency, and duration of their observed symptoms, the participants in these studies are comparable in severity to patients who might typically seek and receive outpatient treatment by mental health professionals for MDD. Studies reported herein do not include depressed patients with psychotic features, patients who are imminently suicidal, or depressed inpatients. Within the context of this book, the included efficacy studies would all be considered type 1 studies. Based on the preceding criteria, only BT, CBT, and IPT have been studied in at least two comparative type 1 outcome trials for outpatients between the ages of 18 and 65 years and, therefore, have been included in this review.

BEHAVIOR THERAPY

Description

Lewinsohn developed the first behavioral treatment program of significance by building on previous behavioral formulations of depression (Ferster, 1973; Skinner, 1953; see Lewinsohn & Gotlib, 1995, for a summary of Lewinsohn's contributions and Cuijpers, 1998, for a meta-analysis of Lewinsohn's BT for depression). Although numerous flavors of BT have been developed for treatment of MDD, they all assume that MDD is related to a decrease of behaviors that produce positive reinforcement. As such, behavior therapies for depression have focused largely on monitoring and increasing positive daily activities, improving social and communication skills, increasing adaptive behaviors such as positive and negative assertion, increasing contingent positive reinforcement for adaptive behaviors, and decreasing negative life experiences (Craske, 2010).

Empirical Evidence

In an RCT, Lewinsohn and his group demonstrated that, relative to various control groups, BT increased pleasant experiences and reduced aversive experiences, and these changes resulted in concomitant decreases in depression severity (see Lewinsohn & Gotlib, 1995). Lewinsohn's work was extended by Bellack, Hersen, and Himmelhoch (1981, 1983) and Hersen, Bellack, Himmelhoch, and Thase (1984), who demonstrated that BT was as effective as the antidepressant amitriptyline in reducing depression over a 12-week treatment period; these effects were maintained over a 6-month follow-up period with six to eight booster sessions.

Extending the behavioral model, Rehm developed self-control therapy (1977) and found it to be superior to nonspecific psychosocial treatments and no-treatment controls (Rehm, 1990). It has not, however, been compared with standard antidepressant medication treatment. The apparently essential ingredient (and perhaps the most important contribution) of this self-control therapy is the self-monitoring of thoughts and behaviors (Rehm, 1990), a component that is included in most other empirically supported psychosocial depression treatment protocols that will be discussed in this chapter.

Following upon Rehm's (1977) suggestions, McLean and Hakstian (1979) added problem-solving and self-control procedures to a BT protocol, and they conducted a 10-week clinical trial comparing this expanded BT intervention to relaxation therapy, insight-oriented psychotherapy, and amitriptyline. The BT program was equal or superior to the other treatment conditions. These results were maintained at a 27-month follow-up (McLean & Hakstian, 1990).

Subsequently, there was a hiatus in studies of BT for MDD because, in the development of the Treatment of Depression Collaborative Research Program (TDCRP; Elkin et al., 1989), Beck and his colleagues integrated BT with cognitive therapy (Beck, 1976) and produced CBT for depression (Beck, Rush, Shaw, & Emery, 1979). Thus, there was minimal BT research for nearly 20 years.

Based in part on the earlier BT work and outcomes, Jacobson and his colleagues (1996) developed a contemporary behavioral activation treatment protocol (see Dimidjian, Barrera, Martell, Muñoz, & Lewinsohn, 2011). These investigators, led by Jacobson, tested the hypothesized theory of mechanisms of change in CBT for depression by comparing the full CBT treatment protocol to its component parts: (1) "behavioral activation" and (2) CBT comprising "behavioral activation plus modification of automatic dysfunctional thoughts." The behavioral activation treatment included techniques such as monitoring daily activities, assessment of pleasure and mastery of activities, assignment of increasingly difficult activities, imaging of behaviors to be performed, discussion of specific problems and identification of behavioral solutions to those problems, and interventions to ameliorate social skills deficits. The primary finding of this study (Jacobson et al., 1996) was that behavioral activation, modification of automatic thoughts, and the full CBT intervention were equally effective, both immediately after the 20-session treatment trial and at the 6-month follow-up. Furthermore, behavioral activation performed equally well over a 2-year follow-up period, with patients across the three treatments having equivalent rates of relapse, time to relapse, and number of well weeks (Gortner, Gollan, Dobson, & Jacobson, 1998).

In a follow-up replication study of Jacobson's CBT component analysis, Dimidjian and colleagues (2006) compared a somewhat modified model of behavioral activation, CBT, the antidepressant paroxetine, and pill placebo in a 16-week MDD treatment

trial. In addition to the behavioral activation techniques employed in Jacobson and colleagues' trial, the expanded model emphasized the importance of avoidance and withdrawal, particularly from interpersonal situations and daily routines. The model also stressed shifting attention from ruminative thinking toward direct experience. Dimidjian and colleagues randomly assigned 241 individuals to the four treatment conditions. Contrary to a primary hypothesis, the investigators found that, among the more severely depressed patients, behavioral activation and paroxetine were comparably effective treatments, while each treatment significantly outperformed CBT. Furthermore, a significantly greater percentage of participants randomized to expanded behavioral activation reached remission when compared with individuals in either the paroxetine or the CBT condition. However, in a later analysis of 2-year follow-up data from this study, CBT was found to be superior to both behavioral activation and paroxetine in the prevention of relapse; behavioral activation and paroxetine were equally effective (Dobson et al., 2008). As Dimidjian and colleagues note, these findings challenge treatment recommendations that stated that moderate to severe depression necessitates medication. Behavioral activation interventions expanded to include an emphasis on avoidance behaviors and the function of rumination may provide an equally efficacious treatment alternative for moderately to severely depressed patients who prefer not to take antidepressant medications.

Since Dimidjian and colleagues' 2006 replication study, preliminary clinical trials have been conducted using behavioral activation in a variety of patients with MDD. Specifically, studies using small samples have suggested that it may be efficacious in patients with comorbid MDD and posttraumatic stress disorder (Mulick & Naugle, 2010) and in patients with MDD characterized by atypical features (e.g., extreme fatigue, hypersomnia; see Weinstock, Munroe, & Miller, 2011).

Given the high prevalence of MDD in individuals with medical concerns, behavioral activation has been evaluated in individuals with comorbid MDD and obesity. Pagoto and colleagues (2008) found a decrease in symptoms of depression as well as significant weight loss after 12 weeks of behavioral activation. There is some evidence that it may be effectively modified for culturally specific groups, for example Latinas (Kanter, Santiago-Rivera, Rusch, Busch, & West, 2010). Behavioral activation continues to be adapted to non–mental-health settings, such as for use in primary care (Uebelacker, Weisberg, Haggarty, & Miller, 2009) or via computer delivery (Spates, Kalata, Ozeki, Stanton, & Peters, 2013). Further research on adaptations of behavioral activation, including virtual delivery, may allow for easier dissemination and implementation of this evidence-based treatment for depression. Evidence from this body of research suggests that behavioral activation may be broadly effective for many variations in the presentation of MDD.

Cognitive-Behavioral Analysis System of Psychotherapy (CBASP; McCullough, 2000)[1] is a form of BT that has been blended with aspects of problem-solving therapy, particularly as applied to interpersonal situations. CBASP focuses on the consequences of a patient's behavior and the use of social problem solving to address interpersonal difficulties. Keller and colleagues (2000) randomly assigned 681 adults with chronic major depression to 12 weeks of acute treatment with CBASP, the antidepressant nefazodone, or the combination of CBASP and nefazodone. Remitters and responders to acute-phase treatment subsequently entered a 16-week continuation treatment phase. Chronic depression was defined as (a) MDD of at least 2 years' duration; (b) current MDD superimposed on a preexisting dysthymic disorder; or (c) recurrent MDD (with incomplete remission between episodes and a total duration of continuous illness of at least 2 years). The overall rate of response was equivalent in the CBASP and nefazodone groups, although patients receiving nefazodone had a more rapid reduction in depression during the first 4 weeks of treatment. Immediately following treatment, the combination of CBASP and nefazodone was superior to either treatment alone (i.e., monotherapy), and this benefit of combination treatment was sustained through the 16-week continuation phase (Kocsis et al., 2003). A greater proportion of participants who received CBASP and nefazodone, compared with the monotherapy conditions, maintained full or partial remission status through the continuation phase. Findings from the same multiphase investigation suggest that CBASP may also be an effective maintenance treatment to prevent the recurrence of major depression (Klein et al., 2004).

A follow-up (Nemeroff et al., 2003) to the study by Keller and colleagues (2000) has provided interesting results regarding the relative contributions of psychotherapy and pharmacotherapy among depressed

patients who experienced an early-life traumatic event (e.g., sexual abuse, loss of a parent). Nemeroff and colleagues reanalyzed data for the 681 patients in the CBASP depression treatment study. These analyses indicated that among those chronically depressed patients who had experienced early childhood trauma, psychotherapy (CBASP) was superior to nefazodone alone for the outcome of remission. However, this interaction was only significant when depression severity data from the first week of treatment were used and not in analyses of change from baseline (see correction, Nemeroff et al., 2005). Further, the combination of the antidepressant with CBASP resulted in only minimally greater efficacy than CBASP alone. A small pilot study by Schramm and colleagues (2011) followed on the study by Nemeroff and colleagues (2003) by stratifying randomization to CBASP and IPT by childhood trauma severity, thus limiting the confounding effects of differential levels of childhood abuse among treatment conditions. This study found no difference after 16 weeks between CBASP and IPT on change scores on the clinician-rated HRSD (Warren, 1996), but there was a significantly higher likelihood to remit with CBASP when rated on the self-reported BDI (Beck, Steer, & Brown, 1996).

The preceding studies regarding early life trauma and depression need replication with more adequately powered studies in which patients are randomly assigned based on early life abuse. At this point, there is a suggestion that an individual, disorder-specific psychotherapy may be the best initial treatment option for depressed patients who have experienced early-life trauma. It is also important that future studies investigate what the underlying neurobiological pathways of effective CBASP are and how they compare to the mechanisms of change in CBT for major depression (see Heim, Shugart, Craighead, & Nemeroff, 2010).

CBASP has also been recently compared to brief supportive psychotherapy (BSP), IPT, and various antidepressant medications for chronic depression. Kocsis and colleagues (2009) conducted a 12-week augmentation trial testing the additive effects of either CBASP or BSP along with an adaptable pharmacotherapy regimen for individuals with chronic depression nonresponsive or only partially responsive to an initial medication trial. However, in contrast to the previous encouraging findings regarding CBASP, the authors found that neither CBASP nor BSP in combination with antidepressant medication based on an ideographic algorithm significantly enhanced response compared to adjustment of antidepressant treatment alone. Swan and colleagues (2014) have found preliminary data in the United Kingdom supporting the usefulness of CBASP for chronic depression. Findings from these studies suggest that CBASP is likely a valid treatment option for chronic depression.

Behavioral Marital Therapy

Another development in behavioral approaches to the treatment of depression has been the use of behavioral marital therapy (BMT) with individuals who are concurrently experiencing MDD and marital distress. Both O'Leary and colleagues and Jacobson and colleagues demonstrated that standard BMT (Beach, Sandeen, & O' Leary, 1990) was equal to individual CBT for alleviating depression among individuals with both MDD and marital discord (Jacobson, Dobson, Fruzetti, Schmaling, & Salusky, 1991; O'Leary & Beach, 1990). BMT was found to have the added advantage of being superior to individual CBT in reducing marital discord, a finding that argues for the use of BMT with depressed patients who are also experiencing marital discord. Although none of the preceding studies used adequate follow-up procedures to test prophylactic effects of BMT versus individual CBT following successful treatment, a recent study by Bodenmann and colleagues (2008) examined the effects of Coping-Oriented Couples Therapy (a version of BMT), CBT, and IPT on relapse rates in the depressed partner in a marriage dyad. Results showed the lowest relapse rates for the Coping-Oriented Couples Therapy group 1.5 years after the 20-week treatment phase (28.6%, compared to CBT: 42.9% and IPT: 62.5%); however, because there were only 20 participants in each treatment group, this difference did not reach significance. Given that "marital disputes" is the most frequently discussed topic among depressed patients in maintenance therapy (Weissman & Klerman, 1973) and that marital friction is an enduring problem among formerly depressed patients even when they are asymptomatic (Bothwell & Weissman, 1977), it is understandable that successful BMT may reduce the rate of relapse among successfully treated MDD patients in discordant marriages. Unfortunately, BMT has not been evaluated with adequate numbers of severely depressed patients in

discordant marriages to know whether these findings will be applicable to such patients or whether the presence of severe depression will necessitate alternative or adjunctive treatments.

Conclusion

Consistent findings support the efficacy of BT for depression. For several years the findings for BT were overshadowed by outcome studies that focused on CBT and IPT as psychosocial interventions for MDD. However, given the applicability of BT to depressed patients of all age groups and the relative efficacy, efficiency, and endurance of behavioral interventions, as well as the recent results for behavioral activation, CBASP, and BMT, it seems that this was an unwarranted and premature redirection of research efforts. From a historical perspective, it appears to have been due primarily to the sociology of science and the exclusion of BT from the well-publicized and influential TDCRP study (Elkin, Parloff, Hadley, & Autry, 1985) rather than to the relative scientific merit and empirical outcomes of the then-available comparative treatment studies. The past decade has seen an increase in research confirming the efficacy of BT for depression, chronic depression, and depression with various comorbidities. Several recent meta-analyses corroborate this conclusion (Cuijpers, Andersson, Donker, & van Straten, 2011a; Cuijpers et al. 2011b; Cuijpers, van Straten, Andersson, & van Oppen, 2008a; Cuijpers, van Straten, & Warmerdam, 2007; Cuijpers, van Straten, Warmerdam, & Andersson, 2009; van Straten, Geraedts, Leeuw, Andersson, & Cuijpers, 2010), indicating a promising trend in the domain of behavior therapy for MDD.

COGNITIVE BEHAVIOR THERAPY

Description

The most extensively evaluated psychosocial treatment for MDD is Beck's cognitive behavior therapy (CBT) (Beck, Rush, Shaw, & Emery, 1979), alternatively referred to simply as cognitive therapy. CBT is a short-term (16 to 20 sessions over a period of 12 to 16 weeks), directive therapy designed to change the depressed patient's negative view of the self, world, and future. The therapy begins with the presentation of the rationale, which is designed to inform the client of the therapy model and the process of therapeutic change. Subsequent early CBT sessions consist of the implementation of strategies designed to increase behavioral activities. The purpose of such an increase is to allow the monitoring of behaviors and their associated thoughts and feelings; CBT models do not posit behavioral changes to be directly responsible for the desired changes in depression. At about the third week, expanded self-monitoring techniques are introduced to demonstrate the relationship between thoughts and feelings; patients are subsequently taught to evaluate their thoughts for logical errors that include arbitrary inference, selective abstraction, overgeneralization, magnification and minimalization, personalization, and dichotomous thinking (Beck, 1976). About the middle of therapy (around session 8 or 9), the concept of schema, or beliefs underlying negative and positive thoughts, is introduced, and therapy begins to focus on changing those negative schemas that are posited to have been activated, thus precipitating the MDD. Toward the end of therapy (sessions 14 through 16), the focus shifts to termination and the use of cognitive strategies to prevent relapse or a future recurrence of depression.

Empirical Evidence

A number of studies have compared the effectiveness of CBT with several tricyclic antidepressant medications (Elkin et al., 1989; Hollon et al., 1992; Rush, Beck, Kovacs, & Hollon, 1977; Simons, Murphy, Levine, & Wetzel, 1986).[2] With the possible exception of the National Institute of Mental Health's TDCRP study (Elkin et al., 1989), the essential finding in all these studies was that CBT and tricyclic antidepressant medication were equally effective in alleviating MDD among outpatients[3] (Tables 13.1 and 13.2). CBT was also as effective as a monoamine oxidase inhibitor (phenelzine), and more effective than pill placebo, in the treatment of atypical depression (Jarrett et al., 1999). This equal efficacy was also obtained when study physicians were free to prescribe the antidepressant of their choice (and free to switch medications during the treatment trial), provided they prescribed at or above established therapeutic doses (Blackburn & Moore, 1997). Recent meta-analyses continue to show that CBT and antidepressant medications are comparable in treating nonpsychotic

TABLE 13.1 Hamilton Rating Scale for Depression Scores and Percentages "Recovered" for Major Random Clinical Trials Reviewed in This Chapter

	CBT										*IPT*					*BT*						*BMT*	
Study	1	2	3	4	5	9	10[a]	11	13	14	6	3	14	16	17	7	8	5	12	14	16	9	10[b]
N	15	36	37	16	44	12	20	36	24	20	17[c]	47	20	15	75	25	42	47	216	20	14	12	8
Pre	21.2	16.4	19.2	24.8	18.6	–	20.0	18.36	19.2	14.15	17.3	18.9	13.95	23.27[d]	30[d]	22.2	–	17.3	26.4	16.2	23[d]	–	23.4
Post	5.8	9.1	7.6	8.8	6.8	–	4.5	10.25	10.7	9.81	10.2	6.9	3.36	18.87	19.5	7.0	–	6.5	15.1	6.88	11.21	–	7.2
Percentage recovered	–	25[g]	51[h]	50[h]	–	–	–	58[e], 44[h]	33[h]	–	–	55[h]	–	27[f]	21[f]	64[i]	–	–	33[f]	–	64[f]	–	–

	Medications													*CBT Plus Medications*	*BT Plus Medications*		*IPT Plus Medications*		*Placebo Plus CM*		
Study	1	2	3	4	6	7	8	11	12	13	15	17	18	2	12	15	17	18	3	11	17
N	14	203	37	32[b]	20	14	49	36	220	43	94	75	52	65	226	195	67	53	34	36	67
Pre	22.4	16.72	19.2	24.0	16.8	25.5	–	16.75	26.8	20.4	18.37	29.6[d]	21.6	17.8	27.4	19.52	28.8[d]	24.8	19.1	17.42	30.3[d]
Post	9.3	8.58	7.0	8.4	10.0	8.2	–	8.64	14.7	12.3	12.28	13.5	10.6	8.2	9.7	11.29	15.1	7.5	8.8	14.44	17.7
Percentage recovered	–	31[g]	57[h]	53[h]	–	43[i]	–	58[e], 42[h]	29[f]	24[h]	40[f]	36[f]	58[g]	23[g]	48[f]	38.5[f]	36[f]	77[g]	29[h]	28[e], 19[h]	24[f]

[a]Data are only for completers who met criteria for MDD and either presence or absence of marital discord.

[b]Data are only for completers who met criteria for comorbid MDD and marital discord; BMT was less effective for MDD and no marital discord.

[c]Data are available only for all patients who entered and completed at least 1 week of treatment.

[d]Data collected on the Hamilton Rating Scale for Depression 24-item version.

[e]HRSD ≤ 9.

[f]HRSD ≤ 8.

[g]HRSD ≤ 7.

[h]HRSD ≤ 6.

[i]HRSD and BDI ≤ 10.

BDI = Beck Depression Inventory; BMT = behavioral marital therapy; BT = behavioral therapy; CBT = cognitive-behavioral therapy; CM = clinical management; HRSD = Hamilton Rating Scale for Depression; IPT = interpersonal psychotherapy.

Source: List of studies: 1. Rush et al. (1977); 2. Thase et al. (2007); 3. Elkin et al. (1989); 4. Hollon et al. (1992); 5. Jacobson et al. (1996); 6. DiMascio et al. (1979); 7. Bellack et al. (1981); 8. McLean & Hakstian (1979); 9. O'Leary & Beach (1990); 10. Jacobson et al. (1991); 11. Jarrett et al. (1999); 12. Keller et al. (2000); 13. Blackburn & Moore (1997); 14. Bodenmann et al. (2008); 15. Kocsis et al. (2009); 16. 17. Lespérance et al. (2007); 18. Schramm et al. (2007).

TABLE 13.2 Beck Depression Inventory Scores and Percentages "Recovered" for Major Random Clinical Trials Reviewed in This Chapter

	CBT										*IPT*					*BT*						*BMT*	
Study	1	2	3	4	5	9	10[a]	11	13	14	6	3	14	16	17	7	8	5	12	14	16	9	10[b]
N	18	36	37	16	44	12	20	36	24	20	17	47	20	15	75	25	42[c]	48	216	20	14	12	8
Pre	30.3	–	26.8	30.4	28.9	26	26.3	25.83	27.3	26.05	–	25.5	24.75	28.47	29.4[j]	27.1	26.8	29.3	–	24.7	25.43	22	26.4[c]
Post	5.9	–	10.2	7.9	9.7	6	6.5	11.72	19	8.18	–	7.7	6.03	21.27	17.9	7.4	9.7	8.5	–	7.18	10.79	5	7
Percentage recovered	83[d]	–	65[e]	62[e]	57[g]	–	80[e]	53[e]	–	–	–	70[e]	–	–,	–	64[f]	50[g]	50[g]	–	–	–	–	88

	Medications													*CBT Plus Medications*	*BT Plus Medications*		*IPT Plus Medications*		*Placebo Plus CM*		
Study	1	2	3	4	6	7	8	11	12	13	15	17	18	2	12	15	17	18	3	11	17
N	14	203	36	32	20	14	49[e]	36	220	43	94	75	52	65	226	195	67	53	35	36	67
Pre	30.8	–	27.1	31.1	–	29.6	27.2	24.86	–	29.2	–	30.4	30	–	–	–	30.2	28.4	28.1	26.9	31.3
Post	13	–	6.5	10.5	–	12.8	14.2	9.67	–	21.5	–	16.4	13.8	–	–	–	14.8	12.3	11	18.94	20.6
Percentage recovered	36[d]	–	69[e]	56[e]	–	43[f]	25[g]	69[e]	–	–	–	–	–	–	–	–	–	–	51[e]	28[e]	–

[a]Data are only for completers who met criteria for MDD and either presence or absence of marital discord.

[b]Data are only for completers who met criteria for comorbid MDD and marital discord; BMT was less effective for MDD and no marital discord.

[c]Data are available only for all patients who entered and completed at least 1 week of treatment.

[d]BDI ≤ 10.

[e]BDI ≤ 9.

[f]BDI and HRSD ≤ 10.

[g]BDI ≤ 7.

BDI = Beck Depression Inventory; BMT = behavioral marital therapy; BT = behavioral therapy; CBT = cognitive-behavioral therapy; CM = clinical management; HRSD = Hamilton Rating Scale for Depression; IPT = interpersonal psychotherapy.

Source: List of studies: 1. Rush et al. (1977); 2. Thase et al. (2007); 3. Elkin et al. (1989); 4. Hollon et al. (1992); 5. Jacobson et al. (1996); 6. DiMascio et al. (1979); 7. Bellack et al. (1981); 8. McLean & Hakstian (1979); 9. O'Leary & Beach (1990); 10. Jacobson et al. (1991); 11. Jarrett et al. (1999); 12. Keller et al. (2000); 13. Blackburn & Moore (1997); 14. Bodenmann et al. (2008); 15. Kocsis et al. (2009); 16. Lespérance et al. (2007); 18. Schramm et al. (2007).

MDD (e.g., Cuijpers et al., 2013). Furthermore, the combination of pharmacotherapy and psychotherapy showed only a small additive benefit when medicine was added to CBT (Craighead & Dunlop, 2014; Cuijpers et al., 2009).

Typically, 30% to 35% of patients with MDD remit and an additional 30% to 35% show response to a course of CBT, thereby no longer meeting criteria for MDD at the end of treatment. Typically, pre–post changes range from the high 20s to single digits for BDI scores and changes from the high teens/low 20s to single digits for HRSD scores (see Tables 13.1 and 13.2). Furthermore, among the samples studied, CBT appeared to confer some enduring prophylactic effects inasmuch as only 20% to 30% of successfully treated patients relapsed during the first year following treatment. Indeed, 16 weeks of CBT produced a 1-year follow-up success rate that equaled or slightly exceeded that achieved by a full year of antidepressant medication treatment (Dobson et al, 2008; Evans et al., 1992). When added to care as usual (including continuing pharmacotherapy) for MDD patients in remission, CBT significantly reduced the chances of relapse or recurrence. Among patients with five or more episodes in the preceding 2 years, the relapse rate in the CBT condition was 46%, compared with 72% in the care-as-usual condition (Bockting et al., 2005). CBT's maintenance effects are clearly superior to short-term (16 weeks) antidepressant treatment. (Sixteen weeks is not the recommended treatment period, but it is, unfortunately, longer than the actual average length of completed medication treatment in clinical practice; Bull et al., 2002; Nemeroff, 2003; Olfson, Marcus, Tedeschi, & Wan, 2006).

Because the TDCRP study (Elkin et al., 1989) has received so much attention, including its significant role in the development of guidelines (not standards) for treatment of outpatients with MDD (Agency for Health Care Policy and Research [AHCPR], 1993; APA, 2010), it is worthy of special note. This study included 250 outpatients who were randomly assigned to one of four 16-week treatment conditions: CBT, IPT, imipramine hydrochloride plus clinical management (IMP-CM), or pill placebo plus clinical management (PLA-CM). The "CM" component of IMP-CM and the PLA-CM conditions included 20 minutes per week talking with an experienced psychiatrist; CM's additive effects simply are not known.

The results of the TDCRP for those patients who completed treatment generally supported the equality of the three presumed active treatments in ameliorating depression at the end of treatment as measured by a HRSD score of 6 or less (CBT, 51%, IPT, 55%, and IMP-CM, 57%); however, only IPT and IMP-CM produced significantly greater reductions in depression than PLA-CM (29%) over the course of treatment, and only then for a few of the outcome measures (Elkin et al., 1989). Even these acute treatment effects were not maintained at the 18-month follow-up: Because the percentages of patients remaining nondepressed and not receiving treatment for depression were quite low (CBT 30%, IPT 26%, IMP-CM 19%, and PLA-CM 20%), none of the active treatments was superior to the PLA-CM condition at the 18-month follow-up (Shea et al., 1992a). These follow-up outcomes indicate that all treatments in this study had considerably weaker effects than had typically been reported in other long-term follow-up studies of these same psychotherapies. Of course, as Klein (1996) has noted, such short-term treatment (16 weeks) with antidepressant medication would not be expected to produce sustained effectiveness.

Based on the original report of the TDCRP data, it has been noted (Hollon, Shelton, & Loosen, 1991), and sustained by reanalyses of the original data tape (Jacobson & Hollon, 1996a), that the lack of unequivocal findings (coupled with the uniqueness of some of the exploratory findings) ensures that any interpretation of the TDCRP data is likely to be controversial. One of the major problems described in the original report of the TDCRP was "consistently significant treatment-by-site interactions for the more severely depressed and functionally impaired patients" (Elkin, Gibbons, Shea, & Shaw, 1989, p. 980). Even though this conclusion has been somewhat attenuated with the use of more sophisticated reanalysis of the data (Elkin et al., 1995, 1996), the general pattern for a treatment-by-site-by-severity interaction is still acknowledged, and the authors conclude: "In regard to the general efficacy of CBT in the treatment of severely depressed (and functionally impaired) outpatients . . . we believe . . . that the answer is not yet in" (Elkin et al., 1996, p. 101).

In their reanalysis of the TDCRP data, Jacobson and Hollon (1996a) underscored the importance of this site-by-treatment-by-severity interaction. They presented data illustrating that at one site CBT did as well as IMP-CM and better than PLA-CM with severely depressed patients (probably not coincidentally, this was also the site at which CBT was rated as

having been conducted at the highest level; see Elkin et al., 1996). At a second site, the data favored either IPT or IMP-CM over both CBT and PLA-CM, with the last two groups not significantly different from one another. At the third site, there were not enough subjects to warrant a comparison. In fact, it is ironic that so much has been made of the findings among the severely depressed patients, since even across three sites there were 15 or fewer severely depressed patients per condition, and "severity" was not taken into account in the random assignment procedure except for the minimal cutoff criterion of 14 on the HRSD.

The essential point regarding the TDCRP is that the findings regarding the appropriateness of CBT alone for severely depressed patients remain inconclusive. Finally, although little has been made of it, there was also a treatment by marital status confound (compounded by differential treatment effects for single and married patients), making interpretation of the data even more difficult (see Jarrett, Eaves, Grannemann, & Rush, 1991; Sotsky et al., 1991).

The TDCRP results played a major role in stimulating work by DeRubeis and colleagues (2005), who conducted a placebo-controlled trial comparing the efficacy of CBT and the antidepressant paroxetine (with lithium or desipramine augmentation, if necessary) for adults with moderate to severe depression. A total of 240 individuals were randomly assigned to a 16-week trial of antidepressant medication, 16 weeks of CBT, or 8 weeks of pill placebo. At 8 weeks, participants in the antidepressant condition displayed significant improvement compared with the pill placebo condition; there was a nonsignificant trend of greater improvement due to CBT compared with pill placebo. At 16 weeks, which marked the end of acute treatment, 40% of the CBT condition and 46% of the medication condition were in remission. When one adds responders (defined as a score of 12 or less on a modified version of the HDRS), 58% of patients treated with CBT and 58% of patients treated with medication met response criteria. Due to a significant site-by-treatment interaction, the findings indicate that with more experienced therapists CBT is as effective as antidepressant medications in treating moderate to severe major depression.

In the associated continuation study of DeRubeis and colleagues (2005), Hollon and colleagues (2005) examined the efficacy of CBT and antidepressant treatment in preventing depressive relapse among the 104 responders of the CBT/antidepressant study. Participants who responded to the antidepressant during the initial 16-week trial were randomly assigned to continuation antidepressant treatment or withdrawal onto pill placebo. Participants who responded to CBT during the acute phase of treatment were asked to refrain from enrolling in additional treatment for depression during the yearlong continuation phase. These participants were allowed up to three booster sessions, at least 1 month apart, during the continuation period. In this investigation, acute treatment with CBT significantly reduced the risk for relapse by 70% compared with the placebo withdrawal group. There was a nonsignificant trend for continuation medication reducing the risk for relapse by approximately 50%. Participants who completed CBT were no more likely to relapse during the 12-month continuation phase than were participants who continued antidepressant treatment, even though the continuation CBT was limited to up to three booster sessions. Overall, these findings indicate substantial, enduring effects of CBT that rival continued pharmacological treatment for severely depressed patients.

CBT can also affect treatment gains for some patients who fail to respond to psychopharmacology. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, Thase and colleagues (2007) studied CBT and several medication alternatives as second-step treatments for patients whose depression failed to remit with initial treatment with citalopram. Patients either switched entirely to the new treatment or received it as an augmentation to citalopram. About 30% of patients who received CBT, either alone or in combination with citalopram, experienced MDD remission, similar to the remission rate among the medication-treated patients.

Recently, strides have been made in employing CBT through virtual means, such as the Internet. Johansson and Anderson (2012) compared a modified form of computer-based CBT, tailored to individual patients according to a treatment plan prepared by a CBT therapist, with standardized virtual CBT and an online discussion group control condition. The authors found, in a sample of 121 outpatients, that the three treatment modalities led to similar significant decreases in depressive symptoms, but that the tailored treatment showed greater effect for those patients with higher baseline depression severity and increased comorbidity.

Continuing CBT after the end of acute treatment can help maintain treatment gains and prevent relapse or recurrence. A meta-analysis of four maintenance studies found that continuation CBT reduced the chance of relapse or recurrence 21% over nonactive control conditions (Vittengl, Clark, Dunn, & Jarrett, 2007). The comparison between relapse and recurrence rates in continuation CBT versus active treatments achieved trend-level significance ($p < 0.06$), and patients who had received continuation CBT had a 12% lower risk of relapse or recurrence than patients receiving other active treatments.

Treatments involving adapted CBT principles also show efficacy in preventing recurrence of MDD. Sheets and colleagues developed a 12-week recurrence prevention program integrating CBT and IPT and taught it in a group setting to young adults who had previously experienced MDD (Sheets, Duncan, Bjornsson, Craighead, & Craighead, 2014). During a 2-year follow up, participants completing the program showed a 50% decline in their risk of recurrence compared to participants receiving assessment only.

Another line of investigation includes studies that have provided a full course of slightly varying forms of CBT following successful treatment of MDD with another type of intervention (e.g., medications). For example, Fava, Grandi, Zielezny, Rafanelli, and Canestrari (1996) compared their form of CBT, "well being therapy," with CM following a course of successful antidepressant medication treatment (although patients were responders and not remitters and still had residual symptoms of depression). All patients were withdrawn from antidepressants prior to the maintenance phase. As has been typical of short-term antidepressant treatment, the 4-year relapse rate following termination of medications was 70%. In contrast, the relapse rate was 35% for the participants who received the additional 10 sessions of this intervention. The difference had dissipated by the 6-year follow-up (75% CM vs. 50% CBT) and was no longer statistically significant (Fava, Rafanelli, Grandi, Canestrari, & Morphy, 1998).

Paykel and colleagues (1999) evaluated patients who had responded to acute treatment with antidepressants but still had residual symptoms. In contrast to the study by Fava and colleagues (1996), all patients were maintained on therapeutic antidepressant doses during the maintenance phase. Patients were randomized to receive either 20 weeks of CBT or CM with antidepressant medication. At the end of the 20-week maintenance treatment phase, relatively few participants had achieved full remission, but those who received CBT were at a significant advantage (25% remission vs. 13% in CM). Furthermore, across the entire study period (maintenance phase and 1-year follow-up), the combination of continued antidepressant medication with maintenance CBT resulted in a lower rate of relapse (29%) than did continued CM with an antidepressant (47%).

A few recent studies have evaluated Mindfulness-Based Cognitive Therapy (MBCT) for the prevention of relapse/recurrence of MDD after discontinuation of antidepressants. MBCT is an eight-session group intervention based on the combination of a mindfulness-based stress reduction program (Kabat-Zinn, 1990) and components of CBT for depression. Teasdale maintained that the critical variables to change in CBT are styles of "thinking about thinking" rather than the content of irrational thinking. Thus, MBCT, while targeting thought processes, helps participants become more aware of and relate differently to their cognitive experiences (Segal, Williams, & Teasdale, 2002). In this sense, MBCT is an extension of Rehm's (1977) emphasis on self-monitoring of thoughts and behaviors in his self-control therapy. A meta-analysis of six RCTs evaluating MBCT for the prevention of relapse or recurrence of MDD found that patients with three or more previous depressive episodes had a 34% lower chance of relapse/recurrence than patients in placebo or treatment-as-usual conditions. Two of the six studies compared MBCT to maintenance antidepressant treatment and found MBCT to be at least as effective (Piet & Hougaard, 2011).

Conclusion

Given the substantial number of studies supporting the efficacy of CBT with patients diagnosed with MDD, it is concluded that CBT is a viable treatment of choice for patients with MDD.[4] Data to date indicate that CBT confers resistance to relapse of MDD whether it is presented as the primary treatment or given as a supplement following successful treatment via some other intervention. MBCT seems especially effective in preventing recurrence among patients with greater numbers of lifetime depressive episodes. Given the widely varying outcomes across studies and the apparent differential competence with which the therapy was delivered across sites in two multisite

studies, it is particularly important that therapists delivering CBT be well trained before they undertake the therapy with patients and that their competence in delivering the therapy be evaluated throughout the intervention phase of any clinical trial of CBT.

INTERPERSONAL PSYCHOTHERAPY

Description

Interpersonal Psychotherpay (IPT) was originally developed as a time-limited (12 to 16 weeks), weekly intervention for unipolar, nonpsychotic MDD (Klerman, Weissman, Rounsaville, & Chevron, 1984). The IPT model derived in large part from Sullivan's interpersonal theory (1953) and the psychobiological theory of Meyer (1957), with its emphasis on the reciprocal relationship between biological and psychosocial facets of psychopathology. Although the IPT model "makes no assumptions about the causes of depression" (Klerman & Weissman, 1993, p. 6), it does suggest that the patient's interpersonal relations may play a significant role in both the onset and the maintenance of MDD. Accordingly, IPT focuses on the identification and amelioration of the patient's difficulties in interpersonal functioning associated with the current MDD. The primary problem areas targeted include unresolved grief, interpersonal disputes, role transitions, and interpersonal deficits (e.g., social isolation).

Empirical Evidence

As shown in Tables 13.1 and 13.2, there have been five reported RCTs of IPT for the acute treatment of MDD in middle-aged adults and one RCT with responders to pharmacotherapy treatment for depression. Three of these studies included long-term follow-up assessments designed to evaluate the prophylactic effects of acute IPT treatment. In addition, there have been two separate controlled studies of "maintenance" IPT following remission of the MDD and one type 1 study of ethnic minority women receiving IPT.

The first RCT of IPT for the acute treatment of MDD was conducted by the treatment's originators, Weissman and Klerman and their colleagues (DiMascio et al., 1979; Weissman et al., 1979). They randomly assigned 81 patients to treatment with 16 weeks of IPT, amitriptyline, combined IPT and amitriptyline, or a "nonscheduled" (i.e., therapy on request, up to one session per month) supportive psychotherapy control. All three treatments were superior to the nonscheduled control condition, and the combination of IPT and amitriptyline trended toward being more effective than either condition alone.

The second (and most frequently cited) RCT of IPT is the previously summarized NIMH multisite clinical trial, the TDCRP study (Elkin et al., 1989). As noted, the study's principal significant finding concerned the clinical rating of depression as measured by the HRSD. All groups began with a pretreatment mean of about 19 and, using the criterion of a posttest HRSD score of 6 or less, both IPT (55%) and IMP-CM (57%) had a significantly greater proportion of patients who achieved the recovery criterion than was observed in the PLA-CM condition (29%). In a secondary data analysis (Elkin et al., 1995), IPT and IMP-CM were also found to be of comparable efficacy among the subset of patients who were severely depressed (defined as a pretreatment HDRS score of 20 or greater). However, as previously highlighted, the presence in this investigation of either a strong trend or a significant treatment-by-site-by-severity interaction (depending on the analysis) precludes the drawing of definitive conclusions from this finding (Elkin et al., 1996; Jacobson & Hollon, 1996b).

A third RCT compared IPT to CM in the treatment of 124 severely depressed inpatients receiving sertraline as a first-line treatment or amitriptyline if patients had a history of nonresponse to sertraline (Schramm et al., 2007). A modified form of IPT was used and included an increased number of sessions, several sessions of group IPT, and incorporation of family members into several psychoeducational sessions. Compared to CM there was a greater decrease in depressive symptoms after 5 weeks of treatment with IPT. Similarly, more IPT patients than CM patients experienced remission (49% and 34%, respectively). In contrast to the preceding studies, Lespérance and colleagues (2007) found no added benefit of IPT over CM in an RCT of 284 outpatients with comorbid MDD and coronary artery disease. Participants were randomized to one of four groups: IPT plus CM and citalopram, IPT plus CM and placebo, CM only and citalopram, or CM only and placebo. After 12 weeks of treatment, citalopram outperformed placebo in reducing depression symptoms, as measured by the Beck Depression Inventory—Second

Edition (BDI-II; Beck, Steer, & Brown, 1996) and the HRSD. Contrary to expectations, IPT showed no advantage over CM and placebo in decreasing depressive symptoms. Furthermore, CM was superior to IPT for patients who reported low baseline levels of social support and daily functioning, a finding the authors attributed to difficulties for these patients in dealing simultaneously with interpersonal problems and heart concerns, required of IPT, in comparison to regular medical management, which entails fewer demands. However, the implication that CM is superior to IPT may not be generalizable to the wider population of individuals with MDD because participants in this study were concurrently diagnosed with coronary artery disease.

Frank and colleagues (2011) recently compared IPT to escitalopram in the treatment of depressed adult outpatients seeking treatment at two major medical centers, in Pittsburgh, Pennsylvania, and Pisa, Italy. A total of 318 patients who met *DSM-IV* criteria for MDD and who scored at least 15 on the HRSD were randomized to receive either IPT or escitalopram for a minimum of 12 weeks and up to 32 weeks or until remission was reached (defined as a HRSD score of 7 or less for 3 consecutive weeks). Any patient who did not respond (defined as at least a 50% decrease in HRSD score from baseline) after 3 weeks of treatment or did not experience remission by week 12 received a combination of IPT and escitalopram for the remainder of the study. Although IPT monotherapy significantly reduced depressive symptoms after 12 weeks (67.1% of the patients in Pisa and 26.6% in Pittsburgh achieved remission), there was no significant difference between treatment conditions in the number of patients experiencing remission.

An RCT by Reynolds and colleagues (2010) examined the usefulness of IPT in depressed older adults who had partially responded (defined as HRSD scores between 11 and 14) to 6 weeks of escitalopram treatment. After the initial acute treatment phase, participants were randomized to receive 16 weeks of adjunctive IPT or to continue with escitalopram alone. The addition of IPT did not increase the likelihood of remittance, with roughly 50% of both the IPT and non-IPT groups experiencing remission. There was also no difference between the groups in the rate of symptomatic improvement.

After the completion of treatment, patients in the previously cited studies by Weissman and colleagues (1979), TDCRP (Elkin et al., 1989), and Schramm and colleagues (2007) were evaluated longitudinally for several months in a naturalistic follow-up design as a means of examining possible prophylactic effects achieved with the acute therapeutic interventions. In the first study, no prophylactic effect was associated with IPT versus amitriptyline based on a 12-month follow-up (Weissman, Klerman, Prusoff, Sholomskas, & Padian, 1981); however, the authors reported significantly greater adaptive social functioning among IPT patients. The TDCRP study also found no relative prophylactic effects for IPT. Among patients who recovered during acute treatment, the percentages of patients who remained well during the 18 months of follow-up were as follows: IPT (26%), CBT (30%), IMP-CM (19%), and PLA-CM (20%; Shea et al., 1992a). Primarily because of the small number of subjects and corresponding lack of statistical power, there were no statistically significant differences among the groups. Similarly, there were no differences at follow-up; none of the treatments was superior even to PLA-CM. Finally, Schramm and colleagues (2007) found at the 3-month follow-up that significantly fewer patients in the IPT-plus-antidepressant group had relapsed than in the CM-plus-antidepressant group (3% and 25%, respectively), although this difference was no longer significant 12 months after treatment. Between baseline and the 5-year follow-up, the patients in the IPT condition showed a somewhat greater decrease in HRSD-rated depressive symptoms than the CM group, although the difference between these groups at 5 years was not significant (Zobel et al., 2011). Finally, significantly more patients who had received IPT showed sustained remission at 5 years compared to those in the CM group (28% and 11%, respectively).

The IPT protocol has also been used as an ongoing maintenance therapy following recovery from an MDD. Klerman, DiMascio, Weissman, Prusoff, and Paykel (1974) found nearly equivalent prophylactic benefits when patients received either weekly maintenance IPT or amitriptyline over an 8-month follow-up period, with relapse rates of only 17% and 12%, respectively. Among a group of chronic and treatment-resistant depressed patients, Frank and her colleagues (1990) reported a significant decrease in relapse probability associated with monthly IPT maintenance sessions over a 36-month follow-up period. For this sample, however, there was a substantially larger prophylactic benefit associated with maintenance imipramine, with a 36-month relapse

rate of only 18% in the imipramine group compared with 46% in the IPT group. In a later study, Frank and colleagues (2007) examined differences in recurrence between women who experienced remission from recurrent depression randomized to weekly, biweekly, and monthly IPT maintenance sessions. Although the authors found no difference in relapse rates based on the frequency of maintenance visits, women who had experienced remission from IPT monotherapy were less likely to relapse during the 2-year maintenance phase than those who received combined IPT and selective serotonin reuptake inhibitor (SSRI) treatment during the acute treatment phase (26% and 50%, respectively).

Reynolds and colleagues (2006) examined the likelihood of recurrence of MDD during a 2-year maintenance period in patients who experienced partial or full remission from depression. Patients had received both paroxetine and weekly to biweekly psychotherapy treatment for 16 weeks during the acute treatment phase. During the maintenance period, patients were randomized to receive paroxetine or placebo and IPT or CM. Results indicated that the likelihood of remission did not differ between patients receiving paroxetine and IPT (37%) and those receiving paroxetine and CM (35%) (Reynolds et al., 2006). Some debate has surrounded the validity of this study's conclusions due to initial differences in depression severity between these groups (see Bajbouj & Danker-Hopfe, 2006; Dew, Houck, & Reynolds, 2006; Edwards, 2006). Additionally, there was no difference between IPT and CM in improvements in health-related quality of life across treatment (Dombrovski et al., 2007).

Finally, one type 1 study has shown support for IPT for ethnic minority women with depression. Toth and colleagues (2013) randomized ethnically diverse, low-socioeconomic-status mothers into two 14-week treatment groups: an IPT group and an "enhanced community standard" group (these patients received treatment as usual, psychoeducation about MDD, and access to medication and other support services). Growth mixture modeling revealed differences in the trajectories of depressive symptoms from baseline through 8 months of follow-up, with patients in the IPT group showing significant decreases when compared with the enhanced community standard group.

IPT has been used to address a number of different clinical problems, including comorbidities with depression (Markowitz, 2013). IPT has also been adapted for use with adolescents (sometimes called IPT-A), and initial results are encouraging (Mufson et al., 2004).

Conclusion

The data regarding IPT as a treatment alone and in combination with antidepressants for MDD are favorable. Although there are mixed results for the efficacy of IPT as a maintenance therapy, several recent meta-analyses have concluded that IPT appears to be an efficacious intervention for the acute treatment of MDD (Barth et al., 2013; Cuijpers et al., 2009, 2010, 2011a, 2011b, 2011c; Cuijpers, van Straten, Warmerdam, & Andersson, 2008b; van Straten et al., 2010).

PATIENT MODERATORS OF TREATMENT RESPONSE

Although each of the empirically supported interventions reviewed herein (BT, CBT, IPT) has been shown to be efficacious for depressed individuals, treatment response is highly variable from patient to patient, and a growing body of evidence documents the existence of patient characteristics that moderate treatment response. Following is a brief summary of relevant findings.

The amelioration of dysfunctional cognitive phenomena is the sine qua non of CBT. Accordingly, one might expect the subset of depressed patients with high pretreatment levels of dysfunctional, depressotypic cognitions to be especially likely to benefit from CBT. But the very opposite appears to be the case; that is, patients who score *low* on pretreatment measures of depressotypic cognition tend to experience the most favorable responses to CBT (Hamilton & Dobson, 2002; Rector, Bagby, Segal, Joffe, & Levitt, 2000; Rude & Rehm, 1991; Simons, Gordon, Monroe, & Thase, 1995). Furthermore, MDD patients who report low levels of depressotypic cognitions appear to respond preferentially to CBT in comparison with either IPT or pill placebo (Sotsky et al., 1991), a finding consistent with the hypothesis that effective therapies capitalize on patients' preexisting strengths rather than compensate for their presenting weaknesses (Cronbach & Snow, 1977). Other patient characteristics associated with favorable outcomes in CBT include absence of chronic

depression (Hamilton & Dobson, 2002; Howland, 1991), low social relationship dysfunction (Sotsky et al., 1991), high learned resourcefulness (Simons, Lustman, Wetzel, & Murphy, 1985; see also Burns, Rude, Simons, Bates, & Thase, 1994), experience of intact marriage (i.e., nonsingle/nondivorced marital status; Jarrett et al., 1991; Sotsky et al., 1991), absence of co-occurring social phobia (DeRubeis et al., 2005), and increased number of significant pretreatment life events (Fournier et al., 2009).

Several studies of physiological and neural activity have also found predictors of CBT effectiveness, including decreased pupillary response (indicative of emotional stability and executive control; Siegle et al., 2011), low activity in the subgenual cingulate cortex in response to emotional stimuli (Siegle, Ghinassi, & Thase, 2007), high activity in the amygdala in response to similar stimuli (Siegle et al., 2012), left-hemispheric verbal processing advantage (Bruder et al, 1997), efficiency in emotional processing (Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011; Siegle et al., 2012), normal REM latency during sleep EEG (Simons et al., 1995), and baseline hypoactivity in the anterior insula (McGrath et al., 2013)—a region responsible for emotional awareness and decision making as well as cognitive control (see Craighead & Dunlop, 2014). CBT has also been shown to be especially efficacious with highly ruminative patients (Jones, Siegle, & Thase, 2008), which may relate to excessive frontocortical activity in some forms of depression (Goldapple et al., 2004).

Although personality disorder comorbidity has frequently been observed to predict poor response to various antidepressant interventions (Ilardi & Craighead, 1994/1995; Shea, Widiger & Klein, 1992b), there does not appear to be a robust association between personality pathology and unfavorable outcome in CBT (Hardy et al., 1995; Kuyken, Kurzer, DeRubeis, Beck, & Brown, 2001; Shea et al., 1990; Simons & Thase, 1990; although see Fournier et al., 2008, for opposing evidence). In fact, in the TDCRP study, comorbid personality pathology was predictive of poor treatment response in every treatment modality except CBT (Shea et al., 1990). If replicated, this finding would suggest CBT is a treatment of choice (alone or in combination with antidepressants) for the large subset of MDD patients with comorbid personality disorders. Intriguingly in this respect, with preliminary data, CBASP (McCullough, 2000) has been found to be superior to antidepressant medication (nefazodone) in the treatment of depressed patients with a history of childhood trauma (Nemeroff et al., 2003)—itself a potential developmental precursor of personality pathology.

In keeping with the aforementioned capitalization hypothesis (Cronbach & Snow, 1977), the TDCRP study found that patients with particularly low levels of social dysfunction responded more favorably to IPT than to other treatment interventions (Sotsky et al., 1991). Among variables linked to an unfavorable IPT response are higher pretreatment depression severity (Hollon et al., 2005), trait neuroticism (Frank, Kupfer, Jacob, & Jarrett, 1987), cognitive dysfunction (Blatt, Quinlan, Pilkonis, & Shea, 1995; Sotsky et al., 1991), a lifetime history of panic-agoraphobic spectrum symptoms (Frank et al., 2000., 2011), childhood trauma severity (Zobel et al., 2011), symptoms of dementia (Carreira et al., 2008), persistent insomnia (Dombrovski et al., 2008), a fearful attachment style (Constantino et al., 2013), and lack of need for medical assurance, psychomotor retardation, and psychotic features (Frank et al., 2011). Especially high relapse-proneness following a favorable acute response to IPT has been observed among elderly (older than 70) depressed patients (Reynolds et al., 1999). Comorbid personality disorders may also be associated with less effective IPT (Pilkonis & Frank, 1988; Shea et al., 1990). Joyce and colleagues (2007), for example, found that personality pathology, specifically avoidant and schizoid symptoms, predicted poorer response to IPT treatment than to CBT treatment. Some more recent evidence, however, suggests that personality pathology may not relate to remission in IPT (Levenson et al., 2010). Furthermore, differences exist between dimensional and categorical measures of personality disorders such that the former, but not the latter, are associated with longer time to remission in IPT (Levenson, Wallace, Fournier, Rucci, & Frank, 2012), a finding perhaps explained by the increase in power associated with analyses using dimensional symptom measures (see Joyce et al., 2007). Supplementary analyses in the study by Levenson and colleagues (2012) revealed that the association between personality pathology and less effective IPT was driven by symptoms of borderline personality disorder alone.

Although sorely needed, there has been little research on patient characteristics that moderate treatment response to BT for MDD. Two studies have looked at predictors of change in CBASP. Maddux

and colleagues (2009) found that personality disorder diagnoses did not differentially predict success of CBASP versus nefazodone treatment for chronic depression. Arnow and colleagues (2013) suggest that a positive therapeutic alliance early in treatment predicts better response to CBASP, even more than its association with brief supportive therapy. In another relevant investigation, patients who endorsed "existential" reasons for their depression (i.e., attributed the depression to their feeling that life was meaningless) were found to respond less favorably to BT than to CBT (Addis & Jacobson, 1996). Conversely, however, evidence from an RCT suggested that BT may be superior to CBT overall in the treatment of more severely depressed patients (Dimidjian et al., 2006). Finally, the effectiveness of behavioral activation was not moderated by comorbid personality disorders, and this lack of moderation was also shown in a comparison sertraline group (Moradveisi, Huibers, Renner, Arasteh, & Arntz, 2013).

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Although additional research regarding the impact of psychosocial interventions for MDD is still needed, adequate published data exist to permit the conclusion that three forms of psychotherapy—BT, CBT, and IPT—are efficacious first-line interventions for depressed outpatients. This conclusion is consistent with major meta-analytic reports of psychosocial treatments for MDD (Cuijpers et al., 2008a, 2014; Dobson, 1989; Nietzel, Russell, Hemmings, & Gretter, 1987; Robinson, Berman, & Neimeyer, 1990). Recent meta-analyses indicate that for more chronic cases of MDD, a combination of psychotherapy and antidepressant medication treatment may outperform either type of monotherapy (von Wolff, Hölzel, Westphal, Härter, & Kriston, 2012), but otherwise there are no consistent and robust overall differences between antidepressant medications and psychotherapies alone in the treatment of MDD.

Additionally, recent research indicates that BT and CBT interventions may be as effective as antidepressant medications in the treatment of some severely depressed outpatients, excluding those with psychotic symptoms and those who are imminently suicidal. Initial reports on this topic are mixed (e.g., Elkin et al., 1995; Hollon et al., 1992; Schulberg, Pilkonis, & Houck, 1998). The two large, placebo-controlled investigations (DeRubeis et al., 2005; Dimidjian et al., 2006) previously reviewed provide preliminary evidence that psychosocial interventions alone can be as efficacious as antidepressant medications in treating moderately to severely depressed patients.

Despite the established efficacy of the reviewed psychotherapeutic interventions, it now seems clear that about only one third of MDD patients in clinical research studies will experience remission with the first treatment they receive, whether it be a pharmacological or a psychosocial intervention, and an additional one third of MDD patients will show a response that falls short of remission. Unfortunately, a very high percentage of these responders (as vs. remitters) will suffer a relapse or recurrence of MDD in a fairly short period of time (Craighead & Dunlop, 2014). Except for the fairly consistent finding that patients with MDD and comorbid personality or anxiety disorders (see Fava et al., 2008; Smits, Minhajuddin, Thase, & Jarrett, 2012) tend to fare somewhat differentially with various treatments but relatively poorly in all treatments (especially during post-treatment follow-up periods), there is a dearth of research reliably identifying salient clinical and demographic features that characterize the two thirds of patients whose depression is refractory to their first psychosocial treatment. Furthermore, we know very little about whether this subset of initially refractory patients may respond favorably to a second treatment, although reported crossover studies suggest that many individuals who fail to respond to one antidepressant will experience some treatment gains when switched to a different medication (see Nemeroff & Schatzberg, 1998) or CBT (Thase et al., 2007). Recent research has revealed promise in identifying neurobiological markers that predict a differential response to psychotherapy (McGrath et al., 2013; Siegle et al., 2012), but at present there are still few empirical data to guide clinicians in tailoring psychosocial interventions to individuals with MDD.

Treatment outcome research with long-term follow-up has increasingly pointed to high recurrence rates and to the need for continued intervention beyond acute treatment (Mueller et al., 1999). Some (e.g., Andrews, 2001) have even gone so far as to argue that MDD needs to be managed like a chronic disease. Numerous clinical research efforts are under way to improve the sustainability of acute treatment gains. These approaches include a tapered

schedule of psychotherapeutic "booster sessions" in the months following acute treatment (e.g., Frank et al., 1990; Jarrett et al., 1998; Jarrett, Minhajuddin, Gershenfeld, Friedman, & Thase, 2013) and prophylactic programs for recovered patients designed specifically to prevent the recurrence of the disorder (Fava, Rafanelli, Grandi, Canestrari, & Morphy, 1998; Sheets et al., 2013). Programs directed toward preventing an initial episode of depression among "at risk" youths have also shown promising results after up to a year of follow-up (Arnarson & Craighead, 2009, 2011; Beardslee et al., 2013; Garber et al., 2009).

It is now widely believed that psychotherapy treatments and antidepressants for depression affect the brain through different mechanisms (Craighead & Dunlop, 2014; DeRubeis et al., 2005). Psychotherapy, with the possible exception of behavioral activation, is proposed to work on cortical networks to decrease excessive negative emotion-related activity in limbic regions, while psychopharmacological treatments act in part to modify neurotransmitter activity in the limbic system in order to affect cortical regions (see Ochsner et al., 2009). Although research is elaborating on this simple "top-down" versus "bottom-up" model of depression treatment, few studies have used neuroimaging to assess differential changes across treatment modalities (e.g., Brody et al., 2001; Goldapple et al., 2004; Kennedy et al., 2007; Siegle et al., 2012).

As research moves forward, it will be increasingly important to address the question raised by Paul (1969) and determine which patients will most benefit from which treatment or combination of treatments. Identifying genetic, inflammation, and neural biomarkers and their interactions with clinical predictors of treatment outcomes will help increase treatment remission rates and optimize the provision of mental health services. Neuroimaging, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), currently leads in this direction, although researchers are also exploring other methods (Kemp, Gordon, Rush, & Williams, 2008). Recent neuroimaging studies show some promise in identifying neurobiological markers that predict a differential response to psychotherapy (McGrath et al., 2013; Siegle et al., 2012) For example, McGrath and colleagues (2013) found that pretreatment levels of resting-state activity in the anterior insula as measured by PET differentially predicted individual patient outcomes to antidepressant medications or psychotherapy. This study, and most studies identifying biomarkers of treatment response, used post hoc analyses to identify neural factors predicting outcome. It is extremely timely and important that we identify psychosocial and neurobiological markers that differentially predict alternative treatment outcomes; this will require prospective studies using the hypothesized predictive factors to stratify the treatment assignments in clinical research trials.

NOTES

1. Although it might be argued that CBASP is a form of CBT, we have included this study in the BT section. Although there is some focus on cognitive factors associated with depression, this focus is in service of helping the person achieve a behavioral goal; the primary emphasis of treatment is on problem solving and change of interpersonal behavior. "This approach draws on many behavioral, cognitive, and interpersonal techniques used in other forms of psychotherapy. It teaches patients to focus on the consequences of their behavior and to use a social problem-solving algorithm to address interpersonal difficulties. It is more structured and directive than interpersonal psychotherapy and differs from cognitive therapy by focusing primarily on interpersonal interactions (including those with therapists). In this type of psychotherapy, patients learn how their cognitive and behavioral patterns produce and perpetuate their interpersonal problems and learn how to remedy maladaptive patterns of interpersonal behavior" (Keller et al., 2000, p. 1463).

2. Additional comparative outcome trials of CBT have been conducted in other countries with different diagnostic systems; the most notable of these studies are those by Blackburn, Bishop, Glen, Whalley, and Christie (1981); Blackburn, Eunson, and Bishop (1986); and Teasdale, Fennell, Hibbert, and Amies (1984).

3. MDD patients who have psychotic features or are imminently suicidal have been excluded from all these evaluation studies comparing the effectiveness of antidepressant medications and psychosocial treatments.

4. Although space limitations preclude discussion, two topics warrant brief mention: treatment of the elderly and treatment in inpatient settings. Several studies by Thompson and colleagues (Thompson & Gallagher, 1984; Thompson, Gallagher, & Breckenridge, 1987) and one by Steuer and colleagues (1984) have demonstrated that CBT is as effective as antidepressant medication for the treatment of depression among the elderly. Thompson and colleagues (1987) also found that short-term psychodynamic psychotherapy was as effective as CBT and antidepressant medications for depression

among the elderly. There is modest evidence that the presence of Axis II personality disorders predicts poor outcome among these patients (Thompson, Gallagher, & Czirr, 1988). In a study of IPT (a shortened version), Sloane, Staples, and Schneider (1985) compared the efficacy of 6 weeks of treatment with either IPT or nortriptyline in a small sample ($N = 43$) of elderly depressed patients. By the end of treatment, there was a nonsignificant trend for a superior response to IPT; however, this trend was largely due to patients' poor tolerance of medication side effects, and a corresponding high rate of attrition, in the nortriptyline group. Although this study is frequently cited to support the relative effectiveness of IPT, the absence of details on dependent measures and data analytic techniques severely limits the contribution of this investigation.

There are several systematic studies of CBT with MDD inpatients. In a stringent test of the intervention, Thase and his colleagues (e.g., Thase, 1994; Thase, Bowler, & Harden, 1991) treated unmedicated MDD inpatients for up to 4 weeks with daily CBT. Although a large percentage of these patients responded well to CBT, the outcome was poorer for those inpatients whose HRSD scale scores were 25 or higher or who had hypercortisolemia. The other studies (Bowers, 1990; Miller, Norman, Keitner, Bishop, & Dow, 1989) have combined CBT with antidepressant medications, and this combination seems to reduce relapse among such patients if booster sessions of CBT are maintained following hospital discharge.

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14

Psychological Treatments for Panic Disorders, Phobias, and Social and Generalized Anxiety Disorders

David H. Barlow
Laren R. Conklin
Kate H. Bentley

A substantial number of type 1 studies to date have established the efficacy of cognitive-behavioral treatment (CBT) for persons with panic disorder (PD) with or without the presence of agoraphobia; these treatments include some combination of cognitive elements, exposure to interoceptive sensations similar to physiological panic sensations, in vivo exposure, and breathing retraining. Recently, several large effectiveness trials (type 1) have also established successful dissemination of CBT for PD. In addition, a substantial number of excellent studies, largely type 1, have established the clinical efficacy of situational in vivo exposure for patients with moderate to severe agoraphobia. The treatment of choice for specific phobias is also exposure-based procedures, particularly in vivo exposure; this consensus reflects a large number of type 1 studies of these procedures with patients with specific phobias. The most common treatment approaches for social anxiety disorder (SAD) include social skills training (SST), relaxation techniques, exposure-based methods, and multicomponent CBT, with the latter, as well as exposure-based procedures, attaining the highest level of treatment efficacy in type 1 studies. In early controlled trials, most studies comparing different treatment conditions for patients with generalized anxiety disorder (GAD) did not observe differential improvement rates, while reporting that active treatments were superior to nondirective approaches and uniformly superior to no treatment. Recently, however, studies have suggested that CBT is the most successful form of treatment for GAD. Specifically, newer variants of CBT that target intolerance of uncertainty or metacognitive beliefs about worry are showing promising levels of efficacy and superiority to alternative treatment. Finally, transdiagnostic treatments are gaining support for their efficacy across multiple anxiety disorders and increasing the ease with which manualized CBT approaches may be disseminated in the future.

INTRODUCTION

The development of evidence-based psychological treatments has been, perhaps, most evident in the appearance of effective new treatments for anxiety disorders, particularly during the past two decades. Prior to 1970, anxiety disorders were a highly prevalent but ill-defined group of problems subsumed under the general headings of "anxiety neuroses" or "phobic neuroses." Treatment of neurosis was most often carried out in the context of long-term psychotherapy, with little or no evidence available on the efficacy

of this approach (Barlow, 1988; Hayes, Barlow, & Nelson-Gray, 1999). During the late 1960s and into the 1970s, clinical trials began to establish the efficacy of exposure-based treatments for phobic disorders, specifically agoraphobia and specific phobias.

The successful delineation of specific anxiety disorders with the appearance of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)* in 1980 (American Psychiatric Association [APA], 1980) led to the development of more structured and targeted psychological and drug treatments. From the period 1985 through 1995, effective and evidence-based psychological treatments were developed for PD with no more than mild agoraphobia, GAD, and SAD, as well as posttraumatic stress disorder (Barlow, 1996; Barlow & Lehman, 1996). As our knowledge of the psychopathology and pathophysiology of these conditions deepened, substantial improvements were made in these treatments, including those for certain varieties of specific phobia. From 1995 through 2005, additional evidence accumulated on the efficacy and effectiveness of these procedures, particularly from major clinical trials, including those evaluating the separate and combined effects of these approaches and pharmacological treatments. Since 2005, we have begun to make greater strides in identifying effective treatments for GAD that demonstrate superiority to other active treatment conditions—an area of research that had previously lagged behind controlled trials for other anxiety disorders. In addition, researchers have continued to refine our understanding of the efficacy of psychotherapy and medications in combination, alternative treatment modalities such as virtual reality therapy, and transdiagnostic treatments. In this chapter, we systematically review the current status of the evidence regarding efficacious, evidence-based treatments for agoraphobia, PD, specific phobia, SAD, and GAD. This review is followed by a section describing promising transdiagnostic treatments and a brief concluding section on future directions in treatment development and research for the anxiety disorders contained within this chapter.

Empirical studies are evaluated according to a template created by the American Psychological Association to guide the development of practice guidelines (APA, 2002; American Psychological Association Task Force on Psychological Intervention Guidelines, 1995). This template evaluates studies along two axes, one that examines the treatment's efficacy (internal validity) and a second that examines the clinical utility (effectiveness or external validity) of the treatment under consideration. This template is depicted in Table 14.1. The studies held to the most rigorous research standards are classified as type 1 studies, whereas those that fall short of this standard of excellence are classified as type 2 studies. Research studies conducted with more substantial methodological limitations are classified as type 3 through type 6 studies. When available, we will also include the clinical guidelines established by the United Kingdom's National Institute for Health and Care Excellence (NICE), a government agency working within the National Health Service, which uses a rigorous process to identify and consolidate available evidence to set quality standards of care for treatment providers working in the National Health Service.

PANIC DISORDER AND AGORAPHOBIA

Although panic attacks have been discussed in the literature over the centuries (e.g., Freud, 1895/1961), they were largely ignored by the diagnostic system until the past few decades. In fact, the diagnoses of PD and of agoraphobia with panic attacks were not included in the diagnostic system until the publication of the *DSM-III* in 1980 (APA, 1980). In the *DSM-IV* (APA, 1994) and *DSM-IV* text revision (*DSM-IV-TR*; APA, 2000), diagnoses directly related to panic included the related diagnoses of PD without agoraphobia, PD with agoraphobia, and agoraphobia without history of PD. In the fifth and most recent version of this diagnostic system (*DSM-5*; APA, 2013), agoraphobia is considered a disorder in its own right in that it can occur independently of panic attacks, although these attacks frequently accompany agoraphobia and seem to result in the development of agoraphobia in most cases. The *DSM-5* also includes panic attacks as a specifier applicable to any disorder, thereby acknowledging the ubiquity of panic attacks across a variety of conditions (Craske et al., 2010).

Individuals diagnosed with PD report experiencing recurrent unexpected panic attacks that consist of physical symptoms such as racing heart, shortness of breath, dizziness, sweating, and trembling or shaking. Moreover, they experience continued anxiety focused on experiencing future panic attacks and worry about consequences of the panic attacks or changes in their behavior due to the panic attacks. It is the additional

TABLE 14.1 Overview of Template for Constructing Psychological Intervention Guidelines

Efficacy (Internal Validity)	*Clinical Utility or Effectiveness (External Validity)*
1. Better than alternative therapy 2. Better than nonspecific therapy (RCTs) 3. Better than no therapy (RCTs) 4. Quantified clinical observations 5. Strongly positive clinical consensus 6. Mixed clinical consensus 7. Strongly negative clinical consensus 8. Contradictory evidence *Note:* Confidence in treatment efficacy is based on both (a) the absolute and relative efficacy of the treatment and (b) the quality of the studies on which the judgment is made, as well as their replicability. Confidence in efficacy increases from item 8 (lowest) to item 1 (highest).	1. Feasibility a. Patient acceptability (cost, pain, duration, side effects, etc.) b. Patient choice in face of relatively equal efficacy c. Probability of compliance d. Ease of disseminability (e.g., number of practitioners with competence, requirements for training, opportunities for training, need for costly technologies or additional support personnel) 2. Generalizability a. Patient characteristics: cultural background issues, gender issues, developmental issues, other relevant patient characteristics b. Therapist characteristics c. Issues of robustness when applied in practice settings with different time frames and the like d. Contextual factors regarding setting in which treatment is delivered 3. Costs and benefits a. Costs of delivering intervention to individual and society b. Costs of withholding effective intervention from individual and society *Note:* Confidence in clinical utility as reflected on these dimensions should be based on systematic and objective methods and strategies for assessing these characteristics of treatment as they are applied in actual practice. In some cases, randomized clinical trials will exist. More often, data will be in the form of quantified clinical observations (clinical replication series) or other strategies such as health economic calculations.

RCT = randomized clinical trial.

Source: American Psychological Association Task Force on Psychological Intervention Guidelines. (1995, February). *Template for developing guidelines: Interventions for mental disorders and psychosocial aspects of physical disorders*. Washington, DC: American Psychological Association. Reprinted with permission.

anxiety about the attacks, combined with catastrophic cognitions in the face of panic, that distinguish individuals with PD from nonclinical panickers (Craske & Barlow, 2014). Individuals diagnosed with agoraphobia avoid situations for which escape or finding help would be difficult in the event of developing panic-like or other incapacitating, embarrassing symptoms (e.g., vomiting, disorientation, loss of bowel control). Types of avoided situations could include public transportation, crowded shopping malls, restaurants, or movie theaters. Of note, individuals are diagnosed with agoraphobia alone when they experience agoraphobic avoidance due to anxiety focused on specific somatic symptoms, some of which may be defining symptoms of a panic attack yet have never met criteria for a full, unexpected panic attack. Clinically, patients presenting with agoraphobia only may be treated with protocols intended for patients with PD, and they will usually benefit from such treatment (Craske & Barlow, 2014).

Reports on the prevalence of isolated panic attacks, PD, and agoraphobia vary somewhat across ages. The National Comorbidity Survey Replication (NCS-R), which was conducted in the United States and used the *DSM-IV* criteria, cited lifetime prevalence rates among adults for isolated panic attacks at 28.3% and for PD at 4.7% (Kessler et al., 2006). This same report noted the lifetime prevalence of panic attacks with agoraphobia at 0.8% and PD with agoraphobia at 1.1% among adults. Both PD and agoraphobia have been estimated to have lower lifetime prevalence among older (ages 65+) than younger adults (Kessler et al., 2012), which may be explained by a true decrease in prevalence among older adults,

underreporting due to forgetting among older adults, or sample selection bias (e.g., exclusion of elderly with high morbidity and early mortality).

Finally, it seems that many more women than men experience these disorders. One meta-analysis found that fully three fourths of the participants in research studies on the treatment of the PDs are women (Gould, Otto, & Pollack, 1995), and the NCS-R found the lifetime prevalences of PD and agoraphobia among women to be significantly greater than those for men (7.0% and 3.2% vs. 3.3% and 2.0%, respectively; Kessler et al., 2012). The most common explanation for this marked sex difference in prevalence involves differences in the socialization of men and women (Wolitzky-Taylor et al., 2010). In most cultures around the world, it is more acceptable for women to report fear and to avoid various situations due to it than men, who are expected to minimize their fears and overcome avoidant tendencies regardless of the cost, and often turn to alcohol to self-medicate their anxiety and panic (Barlow, 1988, 2002).

Most individuals with PD can clearly recall life stressors that occurred around the time they experienced the onset of their panic attacks. One study noted that 72% of patients with PD reported life stress existing when their panic attacks began (Craske, Miller, Rotunda, & Barlow, 1990). Moreover, patients with PD often experience other Axis I disorders concurrent with their PD (e.g., Brown, Campbell, Lehman, Grisham, & Mancill, 2001a; Roy-Byrne, Craske, & Stein, 2006). Specifically, results from one study indicated that 60% of patients presenting with PD also met criteria for an additional anxiety and/or mood disorder; further, when presence of a disorder is examined over the lifetime, this rate increased to 77% (Brown et al., 2001a). A recent meta-analysis of 125 empirical papers found that up to 47% of patients with PD (with or without agoraphobia) are also diagnosed with a personality disorder, most commonly avoidant, dependent, or obsessive-compulsive personality disorder (Friborg, Martinussen, Kaiser, Overgard, & Rosenvinge, 2013).

Our own model of etiology, referred to as the "triple vulnerabilities model" (Barlow, 2002; Barlow, Ellard, Sauer-Zavala, Bullis, & Carl, 2014a), posits a nonspecific biological predisposition to experience stress or emotionality and possibly a separate heritability for a low threshold to experience panic attacks (the first vulnerability). Specifically, this generalized biological predisposition, combined with early development of a sense of uncontrollability over potentially threatening life events (a generalized psychological predisposition, the second vulnerability), creates a diathesis. The later experience of life stress then triggers an unexpected panic attack, and in those with first and second vulnerabilities (the diathesis), and a specific learned psychological vulnerability to focus anxiety on "dangerous" somatic symptoms (the third vulnerability), anxiety becomes focused on the next possible panic attack, and PD subsequently develops. Agoraphobia may then follow as a complication of PD in a large proportion of these individuals, mostly women (Barlow, 1988, 2000, 2002; Barlow, Chorpita, & Turovsky, 1996). Empirical investigations conducted in large samples of individuals with PD have supported the existence of such a triple vulnerabilities model (e.g., Bentley et al., 2013; White, Brown, Somers, & Barlow, 2006).

In this section, we first review the development and evaluation of early treatments for agoraphobia and then provide a description of the development and evaluation of psychological treatments targeting PD. More cost-effective treatments are reviewed, as well as translational research (effectiveness studies). Finally, combination treatments are discussed, as well as future directions in treatment development and assessment for these disorders.

TREATMENT OF AGORAPHOBIA (SITUATIONAL IN VIVO EXPOSURE)

There has been a longstanding controversy regarding the nature of the relationship between PD and agoraphobia (Barlow, 2000). As we have noted, the *DSM-III* considered agoraphobia to be a separate phobic disorder (APA, 1980); with the publication of the *DSM-III-R* (APA, 1987), however, agoraphobia was viewed as diagnostically secondary to PD. This change was primarily the result of findings that suggested that, in clinical samples, agoraphobia typically developed as a result of the experience of panic attacks or limited symptoms attacks (Craske & Barlow, 1988; Turner, Williams, Beidel, & Mezzich, 1986). The next two iterations of the *DSM* (*DSM-IV* and *DSM-IV-TR*) included PD with and without agoraphobia, as well as agoraphobia without phobic disorder. The inclusion of agoraphobia without phobic disorder spurred much debate about whether this syndrome actually

exists (Barlow, 2000); however, accumulating evidence indicates that agoraphobia can exist independently of PD, panic attacks, or panic-like features (Wittchen, Gloster, Beesdo-Baum, Fava, & Craske, 2010). Studies also show that agoraphobia in the absence of panic-like features is associated with levels of impairment and disability equal to PD without agoraphobia, and that key differences between agoraphobia and PD in incidence and response to treatment exist (Wittchen et al., 2010). Given that from 1987 until 2013 agoraphobia was only diagnosed within the context of PD or panic-like features, the development of treatments specifically designed to address agoraphobia occurred primarily in the 1960s and 1970s. However, acknowledgment of PD and agoraphobia as distinct, albeit highly comorbid, conditions in the *DSM-5* suggests that we may witness increased focus on the development and testing of treatments to target agoraphobia in its own right.

One initial treatment for agoraphobia was systematic desensitization. This procedure involved imaginal exposure to feared situations coupled with muscle relaxation. Systematic desensitization was originally used because it was believed that actual exposure to feared situations (situational in vivo exposure) might be too intense and would have deleterious effects. Studies conducted to examine the efficacy of systematic desensitization consistently found this approach to be largely ineffective (Gelder & Marks, 1966; Marks, 1971). During this same era, researchers began to treat patients with agoraphobia successfully by conducting graded situational in vivo exposure exercises (Agras, Leitenberg, & Barlow, 1968). In this procedure, patients under the supervision of a clinician were expected to engage in exposure practices by which they systematically ventured away from places they considered "safe" and into the situations they had been avoiding.

During the next several years, situational in vivo exposure continued to be evaluated and was found to be more effective than no treatment or attentional control procedures (Barlow, 1988, 2002; Jansson & Öst, 1982; Mavissakalian & Barlow, 1981). Situational in vivo exposure treatment routinely begins with the patient creating a hierarchy of feared situations or activities that have been consistently avoided (e.g., driving out of a safety zone, shopping in a crowded mall alone, seeing a movie in a theater). Patients are then encouraged to repeatedly enter and remain in these feared situations, using therapeutic coping procedures learned during sessions. Although patients with more severe agoraphobia may require the presence of their therapist during initial exposures, most patients are able to conduct these exercises either alone or with a friend or family member who acts as a supportive coach (Barlow, 1988, 2002).

Throughout the past few decades, researchers have examined the clinical efficacy of situational in vivo exposure using the highest methodological standards. Nearly all these studies fall into the top two categories of the internal validity axis (Axis 1) of the APA template; moreover, the majority also can be characterized as type 1 studies according to the classification system of this volume. These studies have consistently shown the efficacy of situational in vivo exposure; the current consensus is that situational in vivo exposure is an effective treatment for agoraphobia whether or not a PD diagnosis is present (Craske & Barlow, 2014).

Several reviews and meta-analyses conducted primarily in the 1980s found that 60% to 75% of patients who completed situational in vivo exposure treatments show evidence of clinical improvement (Barlow, 1988, 2002; Jacobson, Wilson, & Tupper, 1988; Jansson & Öst, 1982; Munby & Johnston, 1980; Trull, Nietzel, & Main, 1988). Yet while relatively few of these patients were completely symptom-free at the conclusion of their exposure treatment, the clinical gains that were achieved were maintained at long-term follow-up. For example, Jansson, Jerremalm, and Öst (1986) reported maintenance of gains and some continued improvement at a 15-month follow-up. Burns, Thorpe, and Cavallaro (1986) also noted continuation of gains up to 8 years following treatment, albeit punctuated by brief setbacks. More recently, Fava and colleagues (2001) published long-term follow-up data from 132 patients treated with an exposure-based treatment for agoraphobia. This study is classified as type 2 due to the lack of a comparison group. Treatment was delivered in 12 biweekly 30-minute sessions over 6 months; the follow-up period ranged from 2 to 14 years across patients, with a median of 8 years. Findings showed that 23% of patients experienced a relapse at some time during follow-up. Survival analysis also indicated that 93% of patients remained in remission for at least 2 years after treatment, 82% after 5 years, 79% after 7 years, and 62% after 10 years. These results were consistent with a similar long-term follow-up study

of 90 patients previously conducted by the same research group (Fava, Zielezny, Savron, & Grandi, 1995). Additional results from Fava and colleagues (2001) indicated that residual agoraphobia and having a comorbid personality disorder were associated with poorer outcome; additionally, pretreatment depressed mood and the use of psychotropic drugs were identified as significant predictors of relapse.

Results from another type 2 study also support the efficacy of exposure treatment in individuals with agoraphobia. In a study by Peter and colleagues (2008), 42 female patients with agoraphobia were followed for 3 to 9 years (mean of 6 years) after receiving a course of in vivo exposure treatment delivered in individual or group format. Treatment consisted of five 4-hour exposure sessions (four therapist-aided and one self-conducted), as well as exposure homework. Following treatment, 40% of patients were classified as in complete remission at follow-up and 35% met criteria for mild to moderate agoraphobia. Over the follow-up period, approximately two-thirds of patients maintained their posttreatment status, whereas 21% experienced improved agoraphobic symptoms and 14% experienced a worsening of agoraphobic symptoms.

Strategies to Improve the Effectiveness of Exposure-Based Procedures

Researchers have tried a number of strategies to improve the effectiveness of situational, in vivo, exposure-based treatments (Meuret, Wolitzky-Taylor, Twohig, & Craske, 2012). For example, a number of studies attempted to determine whether adding relaxation training to situational in vivo exposure would improve the clinical efficacy of the situational in vivo exposure. In most of these studies, the combined treatments were no more effective than situational in vivo exposure alone (Michelson, Mavissakalian, & Marchione, 1988; Öst, Hellström, & Westling, 1989; Öst, Jerremalm, & Jansson, 1984). Additionally, controlled studies examining the effectiveness of situational in vivo exposure and breathing retraining have found the combined treatment to be no more effective than situational in vivo exposure alone and that it may actually detract from optimal treatment outcomes (Bonn, Readhead, & Timmons, 1984; Craske, Rowe, Lewin, & Noriega-Dimitri, 1997; De Ruiter, Rijdken, Garssen, & Kraaimaat, 1989; Schmidt et al., 2000). When considering the use of these added elements, one must consider the potential for that element to act as a "safety aid," reducing actual exposure to the anxiety-provoking elements of the stimulus.

Researchers have attempted to improve the efficacy of situational in vivo exposure by adding cognitive therapy components such as paradoxical intention or Beck and Emery's (1985) cognitive therapy. Apart from two notable exceptions (Michelson, Marchione, & Greenwald, 1989; Murphy et al., 1998), the current consensus is that combining cognitive elements with exposure generally does not result in added benefit over exposure alone for the treatment of agoraphobia (Craske & Barlow, 2014). Researchers have also manipulated the pace of situational in vivo exposure treatment to identify the approach with maximum therapeutic gains; specifically, massed and intensive exposure sessions have been compared with spaced and graduated exposure sessions (Barlow, 1988, 2002). Generally, studies have not found important differences between graduated, spaced situational in vivo exposures and intensive, massed situational in vivo exposures conducted throughout 4 to 10 days, during which individuals were expected to experience feared situations for several hours each day (Craske & Barlow, 2014; Feigenbaum, 1988). Another important component to consider when seeking to maximize the efficacy of exposure is how to optimize learning during exposure trials. Early perspectives suggested that habituation of fear responding within exposure trials was necessary for long-term corrective learning over repeated exposure sessions (e.g., Foa & McNally, 1996); however, recent research suggests that learning does not necessarily require habituation during individual trials or even between sessions (e.g., Craske et al., 2008; Craske, Liao, Brown, & Vervliet, 2012). The current consensus is that fear toleration, which may involve maintaining high levels of fear and anxiety during exposure trials, rather than fear reduction (i.e., waiting for declines in fear levels) is a primary goal of exposure therapy for PD and other related conditions (e.g., Deacon et al., 2013). Other research emphasizes preventing or removing safety behaviors or signals (e.g., medication, drink, trusted person), providing stimulus variability (e.g., varying intensity levels, durations, settings), and including retrieval cues (e.g., wristbands) as other variables to consider during exposure trials (e.g., Helbig-Lang & Petermann, 2010; Mystkowski, Craske, Echiverri, & Labus, 2006; Rowe & Craske, 1998).

Researchers have also focused their attention during treatment on the interpersonal support systems of persons with agoraphobia as a means of further improving treatment outcome. Because agoraphobia, at its more severe levels, produces a great deal of dependency, researchers theorized that the incorporation of spouses or partners in treatment might facilitate the treatment process. Barlow, O'Brien, and Last (1984) compared exposure treatment with and without spousal involvement in sessions and found that spousal involvement significantly improved treatment effectiveness for a number of women with agoraphobia (with spouses, 86% were treatment responders; without, 43%). Additionally, Arnow, Taylor, Agras, and Telch (1985) examined the effectiveness of communication skills training with spouses or partners by adding it to a situational in vivo exposure protocol. The combined communication skills training and situational in vivo exposure treatment showed greater clinical improvement at both the posttreatment and the 8-month follow-up assessment. Of note, Vos and colleagues (2012) found that treatment focused on interpersonal relationships was less effective than a combination of exposure and cognitive therapy. Collectively, studies support the value of including significant others in treatment of agoraphobia; however, targeting interpersonal contexts without other core components (namely, exposure) may be insufficient.

Briefer Cost-Effective Modifications to Exposure-Based Procedures

Researchers have also studied the effectiveness of more self-directed treatment protocols for agoraphobic avoidance. These studies explore questions raised on the second axis of the APA template mentioned above by examining the clinical utility or external validity of treatments that are typically computer-aided or administered via a workbook or manual (Ghosh & Marks, 1987; Holden, O'Brien, Barlow, Stetson, & Infantino, 1983; Marks, Kenwright, McDonough, Whittaker, & Mataix-Cols, 2004; Schneider, Mataix-Cols, Marks, & Bachofen, 2005; Swinson, Fergus, Cox, & Wickwire, 1995). The results from these studies, along with others (e.g., Andrews, Cuijpers, Craske, McEvoy, & Titov, 2010; Kenwright, Liness, & Marks, 2001; Marks et al., 2003), suggest that delegating traditional therapeutic components (particularly exposure instruction) to self-directed programs, whether administered by computer or telephone, is an efficient, cost-effective method for delivering evidence-based treatment for agoraphobia, unless the patients are too severely phobic, in which case the presence of a therapist seems necessary (Holden et al., 1983).

Another avenue that holds promise for translating traditional exposure-based procedures into more cost-effective treatment is virtual reality (for a review, see Powers & Emmelkamp, 2008). During virtual reality exposure (VRE), artificially created stimuli replace reality within the context of a computerized world. Published studies testing the effectiveness of VRE treatments for agoraphobia have begun to appear in the literature. Although most lack adequately sized samples and control conditions, several recent investigations employing more rigorous methodology are worth noting. In a study by Botella and colleagues (2007), 37 patients (82.9% with agoraphobia) were randomly assigned to VRE, in vivo exposure, or a waitlist condition. Both treatment programs consisted of nine weekly sessions that included psychoeducation, cognitive restructuring, and breathing retraining, exposure with either VRE or in vivo, and relapse prevention. The VRE program included several scenarios simulating a variety of agoraphobic situations and induced bodily sensations similar to those experienced during panic attacks. At posttreatment, there were no significant differences between VRE and in vivo conditions on any outcome variables (including agoraphobic avoidance), and both active conditions significantly outperformed the waitlist at the 12-month follow-up.

One potential weakness of the study by Botella and colleagues (2007) was that both VRE and in vivo exposure contained elements of cognitive therapy and breathing retraining; thus, it was impossible to adequately assess the role of VRE alone. To address this limitation, Malbos, Rapee, and Kavakli (2011) randomly assigned 10 patients with agoraphobia to receive VRE only and VRE combined with elements of cognitive therapy in order to examine the isolated effects of VRE. They found no significant differences between groups on any of the 10 outcome measures at posttreatment. Finally, a recent study conducted by Meyerbroeker and colleagues (2013) examined the effects of four CBT sessions followed by six sessions of VRE, six sessions of in vivo exposure, or a waitlist control condition. Their sample consisted of 55 patients

who met criteria for agoraphobia and PD. Both active conditions resulted in significantly greater improvements than the control, and there were no significant differences between VRE and in vivo exposure on primary outcome measures targeting agoraphobia avoidance and cognitions. Taken together, although initial studies using VRE to treat agoraphobia are promising, further trials using larger samples and a variety of settings are needed to confirm the efficacy of this novel tool.

TREATMENT OF PANIC

Psychological treatments focusing on the unexpected and uncued panic attacks experienced by individuals with PD were developed relatively recently. The majority of these involve CBT (for reviews see Gould et al., 1995; McHugh, Smits, & Otto, 2009; Sánchez-Meca, Rosa-Alcázar, Marín-Martínez, & Gómez-Conesa, 2010), and they share many commonalities. They focus on education about the nature of anxiety and panic, cognitive therapy, and some form of exposure and coping skills acquisition. Of note, the NICE quality standards designate CBT as an evidence-based psychological treatment for PD (NICE, 2011). Some of the more widely used CBT approaches are reviewed here. The studies reviewed in this discussion are categorized as type 1 research unless otherwise noted.

Panic Control Treatment

In the mid-1980s, Craske and Barlow (2007a) developed a psychological treatment protocol for panic attacks now known as *panic control treatment* (PCT). This treatment focuses on exposing the patient to interoceptive sensations similar to physiological panic sensations. PCT also includes a cognitive restructuring component directed at correcting misconceptions about anxiety and panic and evaluating "automatic" cognitions, particularly the overestimations of threat and danger associated with panic attacks. Finally, breathing retraining is incorporated into PCT to correct the tendency of some panic patients to hyperventilate and to provide a meditational calming exercise that can be effectively used by a subset of patients. More recent versions of the treatment discourage the use of breathing retraining because, as discussed earlier in the chapter, there is a possibility for these skills to be misused as a way to avoid the full experience of anxiety. In fact, there is research to show that CBT with breathing retraining is associated with poorer outcomes during follow-up than CBT without breathing retraining (Schmidt et al., 2000).

PCT has been extensively applied throughout the past two decades, with good results (Craske & Barlow, 2014), and has been designated an evidence-based treatment by the Substance Abuse and Mental Health Services Administration (SAMHSA) of the U.S. Department of Health and Human Services through its National Registry of Evidence-Based Programs and Practices program (SAMHSA, 2013). In the first controlled study of PCT (Barlow, Craske, Cerny, & Klosko, 1989), three treatment conditions (PCT alone, relaxation alone, and PCT combined with relaxation) were compared with a waitlist control condition. The relaxation component consisted of progressive muscle relaxation training along with instructions to apply this relaxation when in anxiety-provoking situations. At posttreatment, all three treatment conditions proved to be more effective than the waitlist control condition. Of the patients, 60% in the relaxation condition and 87% in the PCT-alone condition and the PCT-plus-relaxation condition achieved panic-free status by the conclusion of the 15-week treatment. Two years after acute treatment, 81% of the patients in the PCT-alone condition were panic-free compared with only 43% of the patients in the PCT-plus-relaxation condition and 36% of the patients in the relaxation-alone condition (Craske, Brown, & Barlow, 1991). Craske and colleagues suggested that the patients in the PCT-plus-relaxation condition were not able to show evidence of greater therapeutic gains due to the abbreviated nature of PCT in this condition compared to the PCT-alone condition.

Recent years have witnessed several larger-scale trials aimed to rigorously evaluate PCT. In one large multisite study that compared single and combined effects of CBT and imipramine for patients with PD with no more than limited agoraphobia, patients were randomly assigned to receive 3 months of imipramine only, CBT only (PCT), placebo only, PCT plus imipramine, or PCT plus placebo (Barlow, Gorman, Shear, & Woods, 2000). They were then seen monthly in a maintenance condition for 6 additional months (except for nonresponders to the

drug-only condition) and followed for 6 months after treatment discontinuation. The results indicated that all the treatment groups were significantly superior to placebo after the acute and maintenance phases, with some evidence that among those who responded, imipramine alone produced a better quality of response (e.g., less depression). However, PCT plus imipramine was generally not superior to PCT plus placebo immediately following treatment, although there was some advantage for the combined treatment after 6 months of maintenance. But 6 months after treatment termination, significantly more patients in the imipramine-alone group or the PCT-plus-imipramine group relapsed compared with groups receiving PCT without imipramine (PCT alone and PCT plus placebo). This study suggests that PCT produces a more durable response than medication.

One criticism of the majority of research examining the efficacy of PCT is that most treatment trials target participants displaying minimal to moderate levels of agoraphobia, and little is known about the effect of PCT on panic patients with more severe levels of agoraphobia. In an attempt to better target agoraphobia within the context of panic treatment, Craske, DeCola, Sachs, and Pontillo (2003) examined whether PCT with an additional in vivo exposure component would be more effective in treating patients with PD with agoraphobia than traditional PCT alone. Results indicated that the two treatment conditions were equally efficacious, suggesting the additional component added no benefits above and beyond the relatively robust treatment outcome effect of PCT alone. Further, a large-scale trial by Aaronson and colleagues in 2008 ($N = 381$) included participants with moderate to severe agoraphobia to examine whether response rates during PCT differ among these patients. Findings showed that response rates did not differ across individuals with and without agoraphobia and were similar to those in the prior study by Barlow and colleagues (2000) that excluded patients with moderate or severe agoraphobia.

The fourth edition of a comprehensive PCT treatment manual for PD for adults titled *Mastery of Your Anxiety and Panic* (*MAP-4*; Craske & Barlow, 2007a) presents clinicians with a step-by-step guide to conducting the various aspects of PCT therapy. A PCT manual adapted for adolescents (*MAP-A*; Pincus, Ehrenreich, & Mattis, 2008) is also available.

Cognitive Therapy

Both PCT and other forms of CBT, as well as more traditional cognitive therapies, include nearly identical components. Cognitive therapies, naturally, place a greater focus on cognitive components, while PCT emphasizes interoceptive and in vivo exposure procedures. In a controlled trial of cognitive therapy for panic, Beck, Sokol, Clark, Berchick, and Wright (1992) compared the efficacy of 12 weeks of cognitive therapy with 8 weeks of brief supportive therapy. After 8 weeks of treatment, 71% of the patients who received cognitive therapy were panic-free as compared with 25% of the patients who received supportive therapy. Moreover, at posttreatment, 94% of the patients in the cognitive therapy condition were panic-free, and at the 1-year follow-up assessment, 87% of these patients continued to be panic-free. While cognitive therapy has superior performance when compared to brief supportive therapy, other research suggests the strength of its effects is comparable to interoceptive exposure (Arntz, 2002). However, cognitive therapy and interoceptive exposure appear to use different change processes. To this end, Arntz identified the reduction of idiosyncratic beliefs to be an active mechanism of change in cognitive therapy but not interoceptive exposure. In a similar vein, an interesting study by Meuret and colleagues (2010) showed that during a 4-week cognitive training targeting panic-related cognitions, significant changes in symptoms were mediated by changes in symptom appraisal, whereas during respiratory training (but not cognitive training), changes in respiration mediated panic symptom severity.

Clark and his colleagues also developed a psychological treatment for PD consisting of a unique variation of cognitive therapy (Clark, 1989; Salkovskis & Clark, 1991). This treatment attempts to change patients' appraisals of bodily sensations like PCT; however, Clark's approach places a greater emphasis on the cognitive therapy component of the protocol. Results from a variety of controlled studies conducted in different countries have shown that this cognitive therapy program is superior to control conditions, including other active treatments such as supportive therapy, applied relaxation, and imipramine (for a review see Clark, 1999). For example, Clark and colleagues (1994) conducted a randomized controlled trial (RCT) comparing the effectiveness of three active treatments (cognitive therapy, applied relaxation, and

imipramine) to a waitlist control condition. Patients in the active treatment conditions met weekly with a clinician for 3 months and then monthly for 3 months. Posttreatment results showed that all three active treatments were significantly more effective than the waitlist control condition. In fact, the cognitive therapy treatment was superior to the waitlist control condition on all panic and anxiety treatment outcome measures; the applied relaxation condition and the imipramine treatment condition were superior to the waitlist control condition on just over half and fewer than half of the treatment outcome measures, respectively. Moreover, a 9-month follow-up after the discontinuation of treatment showed that the patients in the cognitive therapy condition largely maintained their treatment gains. Of the patients who received cognitive therapy, 85% remained panic-free, while 60% of the patients who received imipramine and 47% of the patients who were treated with applied relaxation were panic-free.

Alternative and Adjunctive Treatments

Although several novel alternative treatments have been evaluated, most recent studies have focused on integrating adjunctive strategies into basic CBT interventions. In 1994, Shear, Pilkonis, Cloitre, and Leon developed a novel treatment approach called *emotion-focused therapy* that focuses on interpersonal triggers for panic attacks rather than interoceptive cues (for a review see Shear & Weiner, 1997). Attrition was high in this first study, but preliminary results were promising. In a further evaluation by Shear, Houck, Greeno, and Masters (2001), patients were randomly assigned to emotion-focused therapy, CBT, imipramine, or placebo. Treatment included approximately 3 months of weekly visits and six monthly maintenance sessions. This study found that emotion-focused therapy was less effective than either CBT or imipramine for symptoms of PD. In addition, results for emotion-focused therapy at postacute and postmaintenance follow-up were similar to placebo. At follow-up, patients receiving emotion-focused therapy fared better than those receiving placebo but less well than those treated with CBT or imipramine.

Panic-Focused Psychodynamic Psychotherapy (PFPP; Milrod et al., 1997), a psychodynamic treatment specifically targeting PD, has been evaluated in two empirical investigations to date. PFPP involves three phases that aim to target acute panic symptoms, panic vulnerability, and treatment termination; it addresses how psychodynamic conflicts and transference, as well as interpersonal relationships, interact to render individuals more vulnerable to experiencing panic. In 2007, following a type 2 pilot study of PFPP ($N = 16$; Milrod et al., 2001), Milrod and colleagues compared PFPP with applied relaxation in its first type 1 trial. Participants ($N = 49$) with PD were randomly assigned to receive 24 twice-weekly sessions of either PFPP or applied relaxation; those in the PFPP condition evidenced significantly greater reductions in panic symptom severity and were more likely to respond at treatment termination. Although further research is needed, these data indicate that psychodynamic approaches may be useful in the treatment of panic.

Turning to adjunctive strategies, recent years have also shown increasing interest in integrating mindfulness- and acceptance-based therapies into the treatment of PD. For example, Kim and colleagues (2009) randomly assigned 63 patients with PD (or GAD) to receive Mindfulness-Based Cognitive Therapy (MBCT; a training program including a combination of mindfulness techniques, cognitive approaches, psychoeducation, and homework) or an anxiety disorder education program for 8 weeks. Both interventions were applied as an adjuvant to ongoing pharmacotherapy. Results indicated that the MBCT group demonstrated significantly more improvement than the education group on all general anxiety and depression scale scores at the posttreatment assessment. Kim and colleagues (2010) sought to extend these findings by conducting another type 2 study with 23 PD patients that included a panic-specific scale. After the 8-week MBCT program (administered as an adjunct to ongoing pharmacotherapy), panic symptom severity, phobic symptoms, anxiety sensitivity, general anxiety, and depressive symptoms were all significantly improved.

In a similar vein, extending approaches that emphasize acceptance (e.g., Acceptance and Commitment Therapy [ACT]; Hayes, Strosahl, & Wilson, 2011) to the treatment of panic has also been subjected to recent empirical investigation. Meuret and colleagues (2012) examined the feasibility and efficacy of four sessions of ACT, which emphasized assuming an open, nonjudgmental stance to thoughts, feelings, and sensations that arise in a given moment, followed by six sessions of more traditional

exposure procedures in a type 2 trial of 11 patients diagnosed with PD. Treatment was associated with clinically significant improvements in panic symptom severity, reductions in avoidant behavior, and willingness to allow inner experiences to occur, suggesting that the use of ACT to facilitate exposure to feared stimuli may be efficacious. Although these initial findings provide support for the contribution of mindfulness- and acceptance-based strategies to the treatment of panic, rigorous type 1 trials are necessary to determine the efficacy of these procedures.

There is also increasing evidence to suggest that aerobic exercise may lead to reductions in anxiety and mood disorders in general (for reviews see Salmon, 2001, and Stathopoulou, Powers, Berry, Smits, & Otto, 2006). Studies have specifically shown that aerobic exercise reduces anxiety sensitivity, a known precursor of panic attacks and PD (e.g., Broman-Fulks, Berman, Rabian, & Webster, 2004; Broman-Fulks & Storey, 2008). For example, in one study, participants were randomly assigned to a 2-week exercise intervention, a 2-week exercise-plus-cognitive-restructuring intervention, or a waitlist control (Smits, Berry, Rosenfield, Powers, Behar, & Otto, 2008). Results showed that both exercise conditions resulted in clinically significant reductions in anxiety sensitivity compared to the waitlist. Aerobic exercise may serve as a more intense form of interoceptive exposure and thus may decrease anxiety associated with bodily sensations similar to the mechanism associated with the interoceptive component of PCT; research that directly compares aerobic exercise with traditional interoceptive exposure is needed. Although newer research suggests some advantage for traditional CBT compared to exercise alone due to greater reductions in some symptoms, such as anxiety focused on bodily sensations (Hovland et al., 2013), the fact that exercise can be easily disseminated across many populations suggests that it is still a practical, useful intervention to consider in the treatment of PD.

As we have noted, there are accumulating data to suggest that breathing retraining is often misused as a means for distracting or otherwise avoiding physical symptoms (e.g., Meuret, Wilhelm, Ritz, & Roth, 2003; Schmidt et al., 2000). While current consensus in the field is that breathing retraining may be useful when it does not serve as a form of avoidance or safety behavior (Craske & Barlow, 2014), recent years have witnessed the development of a related, yet distinct, biofeedback treatment modality—capnometry-assisted respiratory training (CART; Meuret, Wilhelm, & Roth, 2004). CART aims to change breathing dysregulation in individuals with PD. During a 4-week training, patients are taught how to use feedback from a portable capnometer about their PCO_2 (partial pressure of carbon dioxide) levels to raise subnormal levels of PCO_2, thereby better controlling their dysfunctional respiratory patterns and symptoms associated with hyperventilation that are related to panic (e.g., dizziness, shortness of breath; Meuret, Rosenfield, Seidel, Bhaskara, & Hofmann, 2010). This intervention represents a divergence from traditional breathing retraining as it relies on biofeedback and direct manipulation of respiratory physiology (Meuret et al., 2003). Several preliminary studies to date have examined the efficacy of CART (Meuret et al., 2008, 2010). In one controlled trial, PD patients were randomized to receive 4 weeks of CART (n = 21) or cognitive therapy (n = 20; Meuret et al., 2010). Reductions in panic symptom severity and panic-related cognitions, as well as increases in perceived control, were significant and comparable across the two conditions. Further, corrections in hypocapnic levels were only observed in the CART condition, which supports the notion that CART operates through a pathway distinct from other procedures. Although initial results are promising, future studies must evaluate the degree to which CART augments well-established procedures such as exposure therapy in the treatment of PD and that any observed results are specific and causally related to biofeedback.

Finally, some recent trials have examined whether the addition of memory-enhancing medications and cognitive rehabilitation to CBT may contribute to outcomes and perhaps shorten treatment. For example, Otto and colleagues have explored the use of D-cycloserine (DCS), a partial *N*-methyl-D-aspartate (NMDA) agonist, in augmenting brief CBT for panic. DCS has been identified as an augmentation agent that facilitates the extinction of learned fear in laboratory animals and enhances the effects of traditional therapy for anxiety and related disorders (for reviews see Bontempo, Panza, & Bloch, 2012; Hofmann, Wu, & Boettcher, 2013; Norberg, Krystal, & Tolin, 2008). One randomized, double-blind, placebo-controlled augmentation trial compared brief (five-session) CBT augmented with either DCS or pill placebo (Otto et al., 2010). Results indicated large effects for DCS augmentation on PD symptoms and global severity of disorder at posttreatment and 1-month follow-up time

points; however, the between-group difference in clinically significant change was not statistically significant at follow-up. Of note, over half of participants in the CBT-plus-placebo condition met criteria for clinically significant change at follow-up; these findings underscore the effectiveness of five-session CBT without an active memory-enhancing agent. A similar study conducted by Siegmund and colleagues (2011) indicated that although DCS did not improve outcomes for patients with agoraphobia and PD, this mechanism did accelerate symptom reduction during 11 sessions of CBT in severely ill patients. Future research in this realm, such as an ongoing multisite, large-scale trial conducted by Otto and colleagues, may further elucidate the augmenting role of DCS in the treatment of PD.

Briefer Cost-Effective Treatments

Several studies have explored the effectiveness of CBT for PD when it is administered in a more cost-effective manner, such as with limited therapist contact or other self-directed modalities including Internet delivery (e.g., Cote, Gauthier, Laberge, Cormier, & Plamondon, 1994; Newman, Erickson, Przeworski, & Dzus, 2003). These studies address the questions raised on the second axis of the APA template, or the clinical utility or external validity of these treatments.

For instance, Cote and colleagues (1994) conducted a study in which patients were randomly assigned to receive CBT with either a standard amount of therapist contact (weekly hour-long sessions) or reduced therapist contact (twice-monthly hour-long sessions with twice-monthly 10-minute telephone contacts). Results of this study demonstrated that both treatment modalities were equally effective; more than 73% of the patients in both groups were both panic-free and clinically improved at the 6-month follow-up assessment. Other research has produced mixed findings; for example, a study by Sharp and colleagues (2000) showed that patients receiving standard therapist contact evidenced a stronger and more comprehensive treatment response than those receiving minimum therapist contact or self-directed manualized therapy.

Multiple studies have investigated the effectiveness of bibliotherapy, or self-directed treatment using a manual, in the treatment of PD (e.g., Lidren et al., 1994). In fact, the NICE clinical guidelines include bibliotherapy based on CBT principles as a treatment recommendation for individuals with PD (NICE, 2011). In one randomized trial, Febbraro and colleagues (1999) found some additional benefit of bibliotherapy that also included phone contact. This study compared the effectiveness of bibliotherapy alone, bibliotherapy plus phone contact, or phone contact alone. Among the 30 patients who completed the study, individuals in both bibliotherapy conditions showed significant reductions in panic-related cognitions and anxiety focused on panic at posttreatment; however, only individuals in the bibliotherapy-plus-phone-contact group exhibited significant reductions in panic symptoms and avoidance. More recently, Nordin and colleagues (2010) addressed concerns that therapist support is necessary in successful treatment of PD with bibliotherapy by showing that patients receiving unassisted bibliotherapy ($n = 20$) for 10 weeks (with a scheduled follow-up interview) evidenced significantly greater improvements on all outcome measures at posttreatment and a 3-month follow-up than those on a waitlist ($n = 19$). Questions remain about the severity of disorder in this sample.

Recent years have also witnessed other attempts to increase the cost-effectiveness of CBT, such as shortening the traditional treatment duration, which is typically 12 to 15 weeks (for a review, see Otto et al., 2012). This often involves more intense sessions that occur over a shorter time period. Deacon and Abramowitz (2006) examined the effectiveness of a brief (2-day), intensive CBT for PD. They found that 6 out of 10 patients were panic-free after treatment and continued to report nonclinical levels of panic symptomatology at the 1-month follow-up. In a similar vein, Bohni and colleagues (2009) observed comparable panic outcomes between 3 weeks of massed group CBT (daily 4-hour sessions in week 1, two 2-hour sessions in week 2, and one 2-hour session in week 3) and standard, spaced group CBT (13 consecutive, weekly 2-hour sessions) at posttreatment, 3-, 6-, and 18-month follow-ups.

Roberge and colleagues (2008) recently conducted a cost-effectiveness study of CBT for PD with agoraphobia where they compared standard PCT (14 individual sessions), group PCT (14 group sessions), and brief PCT (7 individual sessions at 2- to 3-week intervals). All treatment conditions were shown to significantly reduce symptoms, maintain gains, and

reduce rates of relapse as compared to a waitlist control (Marchand, Roberge, Primiano, & Germain, 2009). Cost-effectiveness analyses showed that both brief and group PCT conditions incurred lower direct and indirect treatment costs than standard PCT. These findings suggest that both group and brief formats are cost-effective alternatives to standard CBT for PD.

Clark and colleagues (1999) investigated the effectiveness of brief cognitive therapy for PD. Forty-three PD patients were randomly assigned to either standard cognitive therapy consisting of up to 12 1-hour sessions in the first 3 months or brief cognitive therapy, where patients attended five sessions in addition to using between-session self-study modules. Both treatments produced significantly better results than a waitlist control group. Taken together, findings suggest that brief interventions for PD that incorporate cognitive or exposure elements (or some combination) are promising alternatives to longer, traditional approaches.

With the advance of technology, researchers have also attempted to use the popularity of the Internet to increase both treatment dissemination and time- and cost-effectiveness (for reviews see Andrews et al., 2010; Richards, Klein, & Carlbring, 2003). Carlbring, Ekselius, and Andersson (2003) randomized 22 patients with PD to receive one of two Internet-based self-help programs (applied relaxation or CBT) plus minimal therapist contact via e-mail. Both conditions resulted in medium to large effects on PD symptoms, anxiety, depression, and quality of life, with no significant differences between groups. Hedman and colleagues (2013) also found Internet-based CBT to be effective in the context of routine psychiatric care for patients with PD. Further, Klein, Richards, and Austin (2006) randomly assigned 55 patients with PD to Internet-based CBT with therapist e-mail contact, therapist-assisted CBT manual with therapist telephone contact, or information control. They found that both CBT treatment groups were effective in reducing panic symptomatology, panic-related cognition, and negative affect. Interestingly, the Internet treatment was found to be more effective than the CBT manual/telephone contact on all outcome measures.

In yet another study, Ruwaard and colleagues (2010) randomly assigned 58 community-based participants with chronic panic-related symptoms to receive either Web-based therapist-assisted CBT or a waitlist. Participants who received Internet-delivered CBT evidenced significantly greater improvements on primary panic-related and general psychopathology outcomes at posttreatment. At a 3-year follow-up, these effects were more pronounced. In another study by Bergström and colleagues (2010), findings indicated that patients who received Internet-delivered CBT (n = 53) or group-administered CBT (n = 60) for PD in a psychiatric care setting evidenced similar reductions in severity of panic symptoms; these effects were maintained at the 6-month follow-up. Other analyses showed that the Web-based treatment had superior cost-effectiveness ratios compared to the group treatment at both posttreatment and follow-up. Carlbring and colleagues (2005) also found that Internet-based CBT self-help treatment (with minimal therapist contact) was comparable to in-person CBT of the same 10-week duration. Collectively, these studies suggest that the Internet may be a practical, cost-effective, and efficacious way of delivering CBT (or its components) for PD. However, more randomized controlled studies are needed to examine whether Internet-based treatments are effective in treating PD associated with severe levels of agoraphobia and diagnostic comorbidity.

Current Status

Table 14.2 summarizes the results of selected influential studies evaluating psychological treatment for PD through 2013. Nearly all these studies are classified as type 1; the studies by Öst, Westling, and Hellström (1993), Aaronson and colleagues (2008), Meuret and colleagues (2008), and Meuret and colleagues (2012) fall into the type 2 category due to an absence of comparison groups. Most studies demonstrate the effectiveness of PCT or similar CBT approaches for patients with PD with or without agoraphobia (compared with either no treatment or credible psychotherapeutic alternatives).

Translational Research (Effectiveness Studies)

Several large type 1 effectiveness studies have now appeared evaluating the clinical utility of CBT procedures delivered under naturalistic conditions in primary care settings (e.g., Rollman et al., 2005). For example, Addis and colleagues (2004) compared the efficacy of PCT to treatment as usual in a managed

TABLE 14.2 Clinical Trials of Cognitive-Behavioral Treatments for Panic Disorder: Intent-to-Treat Analysis

Study	Length of Follow-Up (Months)	Treatment (N)	Significant Comparison (% Panic-Free)		
			% Panic-Free	Other Treatments (Yes/No)	Waitlist (Yes/No)
Klosko et al. (1990)	PT	PCT (*N* = 15)	87	No: AL = 50% Yes: PL = 36%	Yes: 33%
Newman et al. (1990)	12	CTM (*N* = 24) CTNM (*N* = 19)	87 87	– –	
Craske et al. (1991)[a]	24	PCT (*N* = 15)	81	Yes: AR = 36% Yes: PCT & AR = 43%	
Beck et al. (1992)	PT	CT (*N* = 17)	94	Yes: ST = 25%[b]	
Black et al. (1993)	PT	CT (*N* = 25)	32	Yes: FL = 68% No: PL = 20%	
Öst et al. (1993)	12	CT (*N* = 19)	89[c]	No: AR = 74%[c]	Yes: 5%
Telch et al. (1993)	PT	PCT (*N* = 34)	85	–	Yes: 30%
Cote et al. (1994)	12	CBTM (*N* = 13) CBTNM (*N* = 8)	92 100	– –	
Clark et al. (1994)	12	CT (*N* = 17)	76[c]	Yes: AR = 43%[c] Yes: IMI = 49%[c]	
Shear et al. (1994)	6	CBT (*N* = 23)	45	No: NPT = 45%	
Craske et al. (1995)	PT	CBT (*N* = 16)	53	Yes: NPT = 8%	
Barlow et al. (2000)	12	CBT (*N* = 77) CBT + PL (*N* = 63) CBT + IMI (*N* = 65)	31.9 41 26	Yes: PL = 13 Yes: IMI = 19.7	
Arntz (2002)	6	CT IE Total *N* = 69[d]	75 71.4	– –	
Öst et al. (2004)	PT	E (*N* = 25) CBT (*N* = 26)	67 79	– –	
Roy-Byrne et al. (2005)	12	PCT + MED[e] (*N* = 119)	63	Yes: TAU = 38%	
Addis et al. (2006)	24	PCT (*N* = 38)	36.8	No: TAU = 21.4	
Milrod et al. (2007)	PT	PFPP (*N* = 26)	73	Yes: AR = 39	
Aaronson et al. (2008)	PT	PCT (*N* = 381)	44.1	–	
Meuret et al. (2008)	12	CART (*N* = 20)	68	–	
Otto et al. (2010)	1	CBT + DCS Total *N* = 31[d]	75	No: CBT + PL = 53	
Meuret et al. (2012)	PT	ACT + E (*N* = 11)	73	–	

(continued)

TABLE 14.2 (continued)

Study	Length of Follow-Up (Months)	Treatment (N)	Significant Comparison (% Panic-Free)		
			% Panic-Free	Other Treatments (Yes/No)	Waitlist (Yes/No)
White et al. (2013)	12	PCT + M-CBT[f] (*N* = 79)	94.8[g]	Yes: A = 81.6[g]	
Hovland et al. (2013)	12	CBT (*N* = 19)	47.4	Yes: PE = 11.8	–

Al = alprazolam; AR = applied relaxation; CBT = cognitive-behavioral therapy; CBTM = cognitive-behavioral therapy and medication; CBTNM = cognitive-behavioral therapy without medication; CT = cognitive therapy; CTM = cognitive therapy and medication; CTNM = cognitive therapy without medication; IE = interoceptive exposure; E = exposure in vivo; FL = fluvoxamine; IMI = imipramine; NPT = nonprescriptive treatment; PL = pill placebo; PCT = exposure and cognitive restructuring; PT = posttreatment; ST = supportive therapy; TAU = treatment as usual; MED = medication; M-CBT = maintenance CBT; A = assessment; PFPP = panic-focused psychodynamic psychotherapy; PE = physical exercise; CART = capnometry-assisted respiratory training; DCS = D-cycloserine.

[a]Follow-up study of Barlow et al. (1989).

[b]At 8 weeks, which was the end of supportive therapy. At this time, 71% of CT patients were panic-free.

[c]Percentage of patients panic-free at follow-up who had received no additional treatment during the follow-up period.

[d]Study reports the total number of patients who were randomly allocated to two treatment conditions, but not the number of patients in each condition.

[e]Algorithm-based pharmacotherapy provided by primary care physician with guidance from a psychiatrist.

[f]Patients who responded to PCT received 9 months of M-CBT or assessment.

[g] Probability of remaining relapse-free from panic disorder at a 12-month follow-up.

Adapted from Barlow, D. H., & Lehman, C. (1996). Advances in the psychosocial treatment of anxiety disorders: Implications for national health care. *Archives of General Psychiatry*, 53, 727–735.

care setting. This study was unique at the time in that few studies had attempted to examine the efficacy of PCT in traditional treatment settings rather than laboratory settings. In this study, 80 patients diagnosed with PD with or without agoraphobia were randomly assigned either to PCT delivered by a recently trained PCT therapist or to treatment as usual. In this case, treatment as usual involved whatever treatment orientation the therapist felt was appropriate for each individual client. Using a number of treatment outcome variables, the researchers found that although both groups showed a significant decrease in panic symptomatology from pretreatment to posttreatment, among the treatment completers, an average of 49% of those in the PCT group and 18.8% of those receiving treatment as usual achieved significant change from pretreatment to posttreatment. Follow-up data at 1 and 2 years after acute treatment with the same sample (using intent-to-treat analyses) indicated no significant differences between those who received PCT versus treatment as usual (Addis et al., 2006). However, when completer status was added as a moderator, those receiving PCT showed significantly lower levels of panic severity and phobic avoidance and a greater likelihood of achieving and maintaining clinically significant change. In a more recent study, Roy-Byrne and colleagues (2005) identified and treated 232 primary care patients meeting criteria for PD across six primary care clinics that were ethnically and socioeconomically diverse. Patients were randomized to receive 12 weeks of either treatment as usual or CBT that consisted of six sessions of PCT modified for the primary care setting. Up to six follow-up telephone contacts were permitted during the subsequent 9 months. Patients also received a copy of a manual modified for primary care patients, *Mastery of Your Anxiety and Panic: Workbook for Primary Care Settings* (Craske & Barlow, 2007b). PCT was delivered by mid-level behavioral health specialists with little or no CBT experience prior to training for this study. Both groups were also offered pharmacotherapy provided by the primary care physician, with guidance from a psychiatrist, with no differences in the use of drugs across the groups and only about 9% of individuals taking advantage of this option. Nevertheless, PCT resulted in sustained and gradually increasing improvement relative to treatment as usual on PD symptomatology, overall mental health functioning, and disability scales.

With the same sample, Craske and colleagues (2006) conducted a hybrid efficacy-effectiveness trial to examine effects of the intensity of CBT in this primary care setting. CBT intensity was operationalized as number of sessions, follow-up phone calls, and number of cognitive-behavioral coping and exposure strategies. Study therapists were the same midlevel behavioral health specialists with minimal or no CBT experience who were trained to deliver a six-session protocol over a 3-month period (plus six brief follow-up phone calls over the next 9 months). Results demonstrated that CBT intensity was associated with lower anxiety sensitivity at 3 and 12 months; further, the number of booster phone calls was associated with lower levels of anxiety sensitivity and depression, and less phobic avoidance, at 12 months. These data emphasize the importance of dose (and in particular phone contacts) when CBT is implemented in primary care settings.

There is also research to indicate that the intensity of training in CBT for PD makes a difference. Grey and colleagues (2008) compared outcomes from primary care therapists before and after receiving training in CBT. The first set of patients received up to 12 sessions of treatment as usual ($N = 12$). Therapists then underwent a 3-day training workshop in cognitive therapy for PD, followed by 8 months in which they treated PD patients with CBT with ongoing supervision. They then participated in another 1-day workshop and another 8-month period of treating patients with CBT while receiving regular supervision. Participants from the post-CBT-training period ($N = 24$) who received CBT achieved significantly greater improvements on all measures of PD and agoraphobia measures at posttreatment and 6-month follow-up compared to participants receiving treatment as usual. These findings suggest that, with adequate training and supervision, cognitive therapy can be disseminated in primary care settings and can significantly improve panic symptoms.

One study suggests that PFPP can be effectively translated into routine clinical care settings. Beutel and colleagues (2013) randomized 54 patients with PD to receive 24 50-minute sessions of either PFPP or CBT. The CBT intervention was delivered in the same number of therapist hours as PFPP, but sessions varied in length; homework was included. Clinicians were community psychodynamic psychotherapists who attended a training course in PFPP and certified CBT therapists. Patients who had failed to respond to previous pharmacological or psychological treatments were included in the study. Findings showed no significant differences between conditions at posttreatment or follow-up, with both treatments resulting in strong effect sizes.

Psychological Treatments in Combination with Pharmacotherapy

Results from a recent large-scale meta-analysis suggest that, overall, CBT is more effective than first-line pharmacological agents for the treatment of PD (Roshanaei-Moghaddam et al., 2011). However, research on the effectiveness of combined psychological and pharmacological treatment is more mixed. Prior to Barlow and colleagues (2000; discussed above), research in this area focused primarily on combining pharmacotherapy with exposure-based treatments for patients with moderate to severe levels of agoraphobia. Studies that compared the effectiveness of tricyclic antidepressants and exposure-based procedures with exposure alone have, for the most part, shown evidence of superior posttreatment results for the combined treatment (Mavissakalian, 1996; Telch, Agras, Taylor, Roth, & Gallen, 1985). However, these results generally were not maintained at follow-up assessments due to the high incidence of relapse experienced by patients in the combined treatment condition after imipramine had been discontinued (e.g., Mavissakalian & Michelson, 1986). The clinical trial by Barlow and colleagues (2000) of PD with no more than mild agoraphobia showed equivalence of monotherapies, no marked advantage of combining treatments, and more durability of CBT.

Recent meta-analyses in this area continue to show a similar pattern of findings. One meta-analysis of 124 studies testing psychological treatment and/or pharmacotherapy for PD determined that the combination of CBT elements and pharmacotherapy was slightly more effective than CBT alone at posttreatment; however, no significant differences were observed at follow-up (Mitte, 2005). The potential long-term negative effects of a combination approach, such as medication use reducing the motivation to practice CBT skills, impairing extinction learning, or contributing to context-dependent learning (for a review, see Otto, McHugh, & Kantak, 2010), may help explain these findings. In a similar vein, another

meta-analysis determined that the combination of antidepressant pharmacotherapy and psychotherapy (largely CBT) was slightly more effective than antidepressants or psychotherapy alone during the acute treatment phase (Furukawa, Watanabe, & Churchill, 2006). During follow-up, however, the combined approach was similarly effective to psychotherapy but more effective than pharmacotherapy.

Along these lines, Raffa and colleagues (2008) investigated why PCT was less effective in offsetting relapse for individuals receiving active drug compared to placebo, which was contrary to expectations based on previous comparisons during the trial by Barlow and colleagues (2000). One hypothesis was that participants had correctly deduced treatment assignments; thus, those taking imipramine believed they were no longer taking an active drug following discontinuation, which accounted for the increased risk of relapse. However, analyses indicated that the study blind remained intact and thus did not support this hypothesis. The researchers suggest other potential reasons for discrepancies in relapse rates, including attribution of change, state-dependent learning, and return of physical symptoms after discontinuation of the active drug. Overall, there is a need to continue studying effective maintenance strategies for PD, in particular the most effective ways to combine medications with CBT to offset potential relapse (Otto, Smits, & Reese, 2006).

With regard to the cost-effectiveness of combined approaches, a comprehensive analysis of psychosocial, pharmacological, and combined treatments for PD indicated that evidence-based monotherapies produced superior cost-efficacy compared to combined treatments (McHugh al., 2007). Of note, CBT was also determined to be the most durable and cost-effective monotherapy. Another recent study indicated that CBT is more cost-effective than either selective serotonin reuptake inhibitors (SSRIs) alone or the combination of CBT plus SSRI for PD (van Apeldoorn, Stant, van Hout, Mersch, & den Boer, 2014). Thus, it would seem that CBT alone may be a more cost-effective treatment,

Combining CBT with benzodiazepines is generally not recommended based on reports that high-potency benzodiazepines may interfere with and detract from CBT treatment gains (Brown & Barlow, 1995; Otto, Pollack, & Sabatino, 1996). Indeed, NICE quality standards state that benzodiazepines should not be prescribed for the treatment of PD and refer to SSRIs and tricyclic antidepressants as the only evidence-based pharmacological interventions for long-term management of PD (NICE, 2011).

Sequential Strategies and Long-Term Maintenance

Psychological treatments, including modifications of PCT, have been used to help patients discontinue benzodiazepines. Researchers have found that a slow taper of alprazolam in conjunction with 10 to 12 weeks of PCT is significantly more successful at helping patients discontinue alprazolam fully than a slow taper alone (Otto et al., 1993) or a slow taper with routine supportive medical management (Spiegel, Bruce, Gregg, & Nuzzarello, 1994). More recently, Otto and colleagues (2010) randomly assigned 47 patients with PD seeking taper from benzodiazepines to receive PCT (targeting benzodiazepine discontinuation), taper alone, or taper plus relaxation. Results indicated that adjunctive CBT provided significant, large additive benefits above taper alone and taper plus relaxation at a 6-month follow-up. These studies suggest that an innovative combination treatment in which high-potency benzodiazepines are administered initially to those who need immediate relief or otherwise desire medication treatment, followed by psychological treatment such as PCT, may be quite effective for patients with PD. It is possible that the future of combined treatment lies in these sequential strategies as opposed to simultaneous administration of drug and psychological treatment.

Along these lines, clinical investigators have also examined the effectiveness of psychological treatments for patients who were previous nonresponders to pharmacological treatment. For example, Pollack and colleagues (1994) found that 12 weeks of group CBT improved global functioning and panic attack frequency of patients who had shown evidence of an incomplete response to previous pharmacotherapy. Data from one RCT suggest that the combined approach of CBT and antidepressants may be an effective next-step strategy for individuals who do not respond to initial pharmacotherapy (Simon et al., 2009). Taken together, these results (and those from a type 2 trial by Heldt et al., 2006) suggest that there might be a select group of patients with PD who may not benefit from medication treatment but then are able to show evidence of improvement when effective psychological treatments are administered. There

is also some evidence that reversing the sequence for those who initially do less well than expected with CBT by subsequently administering an effective pharmacological treatment produces similar results (e.g., Kampman, Keijsers, Hoogdiun, & Hendriks, 2002; Payne et al., 2013), but additional research is necessary. We know that even those individuals doing well at follow-ups of a year or more with CBT often experience setbacks or other exacerbations of symptoms that occasionally progress to a full relapse (e.g., Burns et al., 1986; Furukawa et al., 2006). In view of the chronicity of PD, there is a need to investigate strategies to prevent relapse.

Based on preliminary studies demonstrating the possible value of maintenance strategies (e.g., Jansson et al., 1986; Öst, 1989), researchers have focused on developing more comprehensive and effective maintenance strategies for preventing exacerbations or full relapse (e.g., Arch & Craske, 2011). For instance, White and colleagues (2013) found that among patients who had responded well to an initial course of CBT for PD, with or without agoraphobia, nine monthly sessions of maintenance CBT, encouraging the continued use of PCT skills and relapse prevention strategies after treatment, reduced the risk of relapse and decreased functional impairment compared to patients who did not receive maintenance CBT. This evaluation suggests that maintenance therapy can be an effective strategy in the long-term management of PD. Further research that examines whether similar effects could be obtained with less frequent or fewer maintenance sessions is needed.

Future Directions

Although CBT approaches to treating PD and agoraphobia are highly efficacious and are becoming more widely accepted, there are still unresolved issues, especially when considering initial resistance by some to treatment and relapse following treatment by others. As a result, researchers have begun to test new combination or sequential treatments to address treatment-resistant individuals and specific maintenance programs for those who have had a successful treatment experience. In addition to brief adaptations of traditional CBT protocols, novel approaches such as mindfulness and acceptance strategies and physical exercise may enhance treatment and perhaps reduce barriers to treatment dissemination for selected individuals. Further, the development of core treatment principles as found in new unified transdiagnostic interventions (Barlow et al., 2011a) may facilitate dissemination. The state of current research on these transdiagnostic approaches will be reviewed in the final section of this chapter.

SPECIFIC PHOBIA

In the *DSM-5*, a specific phobia is defined as a marked and persistent fear cued by the presence or anticipation of an object or situation. The fear must be considered excessive or unreasonable and must be associated with functional impairment or subjective distress. In addition, the specific phobia must not be better accounted for by another *DSM-5* disorder (APA, 2013). The primary characteristics of specific phobia have not been changed from the *DSM-IV* (APA, 1994), which replaced the diagnosis of simple phobia listed in the *DSM-III-R* (APA, 1987).

Five subtypes of specific phobias are included in the *DSM-5:* animal, natural-environmental, blood-injection-injury, situational, and other. The "other" type serves as a catch-all category for specific phobias such as choking or vomiting that do not readily fall into any of the first four subtypes. These subtypes vary according to age of onset, gender composition, patterns of comorbidity, and type of physiological reaction to the phobic situation, as well as other important variables such as natural course and type of treatment indicated. For example, the mean age of onset for animal, blood, storm, and water phobias tends to be in early childhood, whereas the mean ages of onset for situational height and flight phobias are in adolescence (Antony & Barlow, 2002; Becker et al., 2007; Öst, 1987).

The *DSM-5* (formerly *DSM-IV and DSM-IV-TR*) diagnosis of specific phobia, when considered overall, is the most prevalent anxiety disorder (Kessler et al., 2012). Approximately 12.5% of the population has developed or will develop at least one phobia in their lifetime (Kessler et al., 2005). Yet when specific phobias are given as primary diagnoses, the clinician is not likely to observe an additional clinical diagnosis. In other words, principal diagnoses of specific phobias seen in the clinic tend to have lower rates of comorbidity than principal diagnoses of most other Axis I disorders (Moras, Di Nardo, Brown, & Barlow, 1994). Another characteristic of specific

phobia is that people tend to evidence multiple feared objects or situations. In an analysis of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study, Stinson and colleagues (2007) found that, of the 4,030 individuals with a lifetime history of a specific phobia, only 28.9% had a single phobia. The remaining cases had two (21.2%), three (15.9%), four (11.4%), or more than four (22.5%) phobias. The NESARC study also found that animal phobias were the most prevalent, followed by a fear of heights and being in closed places such as an elevator (4.7%, 4.5%, and 3.2% of the population, respectively).

Gender differences are marked in specific phobia, with the lifetime prevalence for women noted to be 15.7% of the population compared with 6.7% for men. Interestingly, this gender difference in prevalence is most pronounced for animal phobia and least apparent for height, flying, and blood-injury-injection phobias (Antony & Barlow, 2002). Women also tend to experience a greater number of types of phobic fear than men (Sigström et al., 2011).

Treatments for Specific Phobias

A consensus has developed that the treatment of choice for a wide spectrum of specific phobias is exposure-based procedures, particularly in vivo exposure. Although imaginal exposure has been shown to produce fear reduction (Baker, Cohen, & Saunders, 1973) and should be used if situational in vivo exposure treatment is not feasible, in vivo exposure is generally accepted as the most powerful treatment for specific phobias (APA, 1994; Antony & Barlow, 2002; Barlow, 1988, 2002; Marks, 1987). The small number of studies that compare in vivo exposure to alternative exposure modalities (e.g., imaginal exposure or in virtuo exposure from virtual reality environments) indicate that in vivo exposure is associated with greater improvements by the end of treatment. However, in vivo exposure and other exposure methods appear more similar in their continued performance during longer follow-up periods (Wolitzky-Taylor, Horowitz, Powers, & Telch, 2008).

In vivo exposure treatment often appears deceptively simple, yet there are many facets to the procedure (Antony & Barlow, 2002). During initial treatment sessions, the therapist gathers more specific information about the patient's feelings, thoughts, and behaviors concerning the phobic object or situation. The patient is informed that systematic, repeated in vivo exposure will allow the patient to become desensitized to the phobic object or situation. The clinician also lets patients know that all in vivo exposures will be predictable and under their control, and he or she teaches patients a variety of adaptive coping strategies to use throughout treatment. Finally, the clinician and patient create a hierarchy of feared situations concerning the phobic object or situation and formulate a treatment plan consisting of in vivo exposure practices.

Extensive literature exists demonstrating the effectiveness of in vivo exposure treatments for specific phobias. Over the past few decades, in vivo exposure has been successfully used to treat most types of specific phobia (Antony & Barlow, 2002). For example, clinical investigators have demonstrated the effectiveness of in vivo exposure to treat phobias of animals (e.g., Öst, 1989; Öst, Ferebee, & Furmark, 1997; Öst, Salkovskis, & Hellström, 1991), heights (e.g., Bourque & Ladouceur, 1980), flying (e.g., Howard, Murphy, & Clarke, 1983; Öst, Brandberg, & Alm, 1997), and enclosed spaces (e.g., Öst, Johansson, & Jerremalm, 1982; Powers, Smits, & Telch, 2004). In addition, in vivo exposure has been used to treat fear of dentists (Jerremalm, Jansson, & Öst, 1986b; Liddell, Di Fazio, Blackwood, & Ackerman, 1994), as well as choking phobia (McNally, 1986, 1994), with good results. Blood-injection-injury phobias also have been successfully treated with in vivo exposure, although these phobias and their treatments are unique and are described below (Öst, 1989; Öst & Sterner, 1987).

Although exposure-based treatments for specific phobias are considered to be fairly straightforward, they are composed of many factors that may have an impact on the clinical results of treatment. These factors include the duration and temporal spacing of exposure sessions, the level of therapist involvement, and the incorporation of additional treatment components into exposure sessions. The following discussion reviews the available empirical evidence regarding these factors.

In general, it appears that massed exposure sessions result in the most robust clinical improvement in specific phobias (for a review of the literature, see Zlomke & Davis, 2008). In as little as one session of therapist-guided exposure, 90% of people with animal or injection phobias and 80% of people with claustrophobia have been found to be much

improved or completely recovered (Öst, 1989; Öst, Alm, Brandberg, & Breitholtz, 2001). In one study, Öst and colleagues (2001) randomly assigned 46 patients with claustrophobia to one of four conditions: one session of exposure (3 hours maximum), five sessions of exposure, five sessions of cognitive therapy, or a waitlist. At posttreatment, 80% of those who received one session of exposure showed evidence of immediate improvement compared to 81% of those who received five sessions of exposure and 79% who received cognitive therapy. All treatments performed better than the waitlist, of whom 18% saw clinical improvement. Results were maintained at a 1-year follow-up; thus, the one-session exposure treatment was the shortest treatment to provide equivalent results.

Rowe and Craske (1998) examined the benefits of an expanding-spaced exposure schedule versus massed exposure. In this model, sessions begin close together and gradually spread out as treatment progresses. They found that massed exposure led to significantly more fear reduction in a group of spider phobics. However, there is mixed evidence regarding which exposure schedule is less likely to be associated with a return of fear following treatment; for example, a replication study by Lang and Craske (2000) did not find a difference between exposure schedules on the likelihood of return of fear. These findings also support new information on the mechanisms of fear reduction alluded to in the previous section, noting that immediate fear reduction is less important than the creation of new memories reflecting successful coping with fear across a variety of situations (Craske et al., 2008, 2012).

The degree of therapist involvement in exposure treatment is also considered to be an important component of treatment for specific phobias. Although relatively few studies have directly examined the influence of the therapist's presence, most empirical findings point to the importance of therapist involvement during exposure (e.g., Hellström & Öst, 1995; Öst et al., 1991). For example, Öst and colleagues (1991) found that whereas 71% of persons with spider phobia improved with therapist-assisted exposure treatment, only 6% of persons who engaged in self-directed exposures evidenced clinical improvement. In a follow-up study, Hellström and Öst (1995) found that the manner in which self-help treatment is disseminated affects the outcome for individuals with spider phobias. In this study, five different treatments were compared: (a) a single session of therapist-assisted exposure, (b) a spider phobia–specific manual used in the home, (c) a spider phobia–specific manual used in the clinic, (d) a nonspecific manual used in the home, and (e) a nonspecific manual used in the clinic. The percentages of individuals who were significantly improved were 80%, 10%, 63%, 9%, and 10%, respectively. These findings suggest that self-help manuals can be beneficial to individuals diagnosed with specific phobias when they are used in a clinic setting.

Other empirical studies have shown that certain types of specific phobias require adaptation of exposure-based procedures that incorporate additional treatment components. For example, individuals with blood-injection-injury phobia tend to have a physiological reaction that can often inspire a fainting response. This physiological reaction, known as *vasovagal syncope*, consists of an immediate rise and fall in heart rate and blood pressure when the person encounters the phobic stimulus. A physical strategy that prevents the fainting response that results from this reaction has been developed and added to exposure treatment. This coping strategy, known as *applied tension*, serves to temporarily sustain the patient's blood pressure and heart rate at an increased level by completing tensing and releasing all large muscle groups (arms, torso, and legs) in 15-second intervals. When patients begin applied tension before the injection procedure begins and continue until after the procedure is over, the possibility of fainting is eliminated. This technique has been empirically validated as an additional component of exposure treatment (Öst & Sterner, 1987). In addition, Hellström, Fellenius, and Öst (1996) showed that a single session of applied tension along with a maintenance program of self-exposure is as effective as a five-session course of the same treatment.

Several treatment manuals for the specific phobias exist. The program developed and manualized at our center presents general information regarding the nature and treatment of specific phobias, as well as detailed treatment information for several of the most common specific phobias (Antony, Craske, & Barlow, 2006). The treatments presented in this manual also incorporate additional treatment strategies to be used in conjunction with in vivo exposure treatments, such as cognitive strategies and interoceptive exposure.

Cognitive strategies are included to combat cognitive distortions and anxious thought patterns, and interoceptive exposures desensitize patients to the physical sensations individuals often associate with the phobic object or situation.

Finally, during the past 10 to 15 years, researchers and clinicians alike have increasingly taken advantage of technological advances for the treatment of specific phobias. For example, a number of investigators have begun to use virtual reality to expose patients to simulated situations such as heights (Rothbaum et al., 1995), flying (Rothbaum, Hodges, & Smith, 1999), and spiders (Carlin, Hoffman, & Weghorst, 1997). Although a large number of studies examining the effectiveness of VRE have been conducted, many lack treatment comparison groups and/or control groups and an adequately large sample size. In the literature to date, controlled trials with larger samples have predominantly been conducted with patients experiencing a fear of flying, spiders, and heights (e.g., Krijn et al., 2004; Michaliszyn, Marchand, Bouchard, Martel, & Poirier-Bisson, 2010; Rothbaum et al., 2006). One meta-analysis conducted by Parsons and Rizzo (2008) found that VRE exhibited large average random effects for the treatment of phobias related to spiders, heights, and flying (range of effects: .92 to 1.59), although some studies analyzed were not RCTs.

Some research has examined whether VRE treatment is equivalent to in-person exposures. For instance, two controlled trials by Rothbaum and colleagues compared VRE treatment, standard exposure treatment, and waitlist for individuals with a fear of flying (Rothbaum, Hodges, Smith, Lee, & Price, 2000; Rothbaum et al., 2006). In both studies, 45 (Rothbaum et al., 2000) and 75 (Rothbaum et al., 2006) patients with a flying phobia were randomized to one of the three treatment conditions. Results from both studies indicated that VRE and standard exposure treatment were both superior to waitlist control, with no differences between VRE and standard exposure. VRE and standard exposure were shown to be effective by decreases in symptoms as measured by standardized questionnaires, by the number of participants who actually flew on a real airplane following treatment, on self-ratings of improvement, and on patient satisfaction with treatment. The gains observed in treatment were maintained at a 6-month follow-up and a 12-month follow-up (in the 2006 study only, as the 2000 study did not have a 12-month assessment). In the earlier study, 93% of VRE participants and 93% of standard exposure participants had flown during the 6-month follow-up. In the later study, 81% of VRE participants and 70% of standard exposure participants had flown during the 12-month follow-up.

Other studies examining the efficacy of VRE treatment for fear of flying have consistently found VRE treatment to be more effective at decreasing fear and avoidance of flying when compared with attention-placebo group treatment (Maltby, Kirsch, Mayers, & Allen, 2002), cognitive treatment, and waitlist control (Mühlberger, Weidemann, & Pauli, 2003). In an interesting version of VRE treatment, Garcia-Palacios, Hoffman, Carlin, Furness, and Botella (2002) randomly assigned 23 patients with a fear of spiders to either waitlist control or VRE treatment with tactile stimulation. In this study, tactile stimulation consisted of patients feeling a "hairy" fabric similar to the sensation of feeling a spider while watching a virtual spider. They found VRE treatment with tactile stimulation to be more effective than waitlist control on all outcome measures, including self-report and behavioral tests.

Although VRE treatments clearly appear to hold some promise as a valuable form of treatment for specific phobias, an important consideration is whether they can generalize to naturalistic settings. One concern is the often substantial number of dropouts that are found in VRE treatment outcome studies (Krijn, Emmelkamp, Olafsson, & Biemond, 2004). Research suggests that the major contributing factor to dropout rates in these studies is the degree to which the patient feels "present" in the experience; this involves feeling that one is in the present world rather than in the virtual world. Krijn and colleagues (2004) found that the reported level of "presence" during VRE treatments was highly correlated with treatment dropout, with lower degrees of "presence" associated with higher dropout rates. In addition, other patient factors such as degree of absorption and hypnotizability may mediate the effectiveness of VRE treatments (Wiederhold & Wiederhold, 2000). As our understanding of the nature of anxiety and technological innovations advances, it is clear that VRE will continue to offer interesting, and perhaps more effective, treatment options for the treatment of specific phobias.

Future Directions

Although a great deal of treatment outcome research exists for specific phobias, much remains to be learned. For example, researchers have only just begun to examine differences among the specific phobia subtypes, and additional information in this area could improve treatments for specific phobias (for a review, see LeBeau et al., 2010). Just as patients with blood-injection-injury phobias benefit from the use of applied tension coupled with exposure therapy, many patients with other specific phobia subtypes might respond more robustly to exposure treatments tailored to their phobic object or situation. For example, treatment may emphasize targeting fears that tend to differ according to subtype. Approximately half of individuals with an animal phobia indicate that the focus of their fear revolves around feelings of disgust and revulsion. In comparison, individuals with natural environment or situational fear subtypes tend to focus their fear on perceptions of danger or harm instead (82% and 52% of those with natural environment and situational phobias, respectively). For individuals with a blood-injection-injury phobia, the focus of the fear tends to be on physical symptoms (37%) and internal feelings such as disgust (37%; Lipsitz, Barlow, Mannuzza, Hofmann & Fyer, 2002).

Moreover, in this era of managed care, when cost-effectiveness is considered to be of utmost importance, further research should be conducted to determine which of the many specific phobias can be treated in just one therapist-assisted in vivo exposure session. Although some information has been gained regarding such intensive treatments for patients with certain animal and injection phobias, as well as blood, claustrophobia, and flying phobias (Hellström, Fellenius, & Öst, 1996; Öst, 1989; Öst, Alm, Brandberg, & Breitholtz, 2001; Öst, Brandberg, & Alm, 1997), more research may help provide support for the efficacy of this treatment modality for other common specific phobias such as elevators, heights, and darkness. One of the best recent examples of research in the domain of single-session exposure treatment was a large multisite RCT conducted with children and adolescents (Ollendick et al., 2009), the quality of which will, it is hoped, be emulated in future treatment research across the lifespan. Lastly, further research should continue to explore the efficacy of virtual reality therapy. Additional controlled trials with adequately large sample sizes and treatment comparison or control groups are still needed, particularly for specific phobias that have not been studied to the extent that fear of spiders, heights, and flying have in the past.

SOCIAL ANXIETY DISORDER

SAD (formerly social phobia in the *DSM-IV*) is estimated to be the second most prevalent of all anxiety disorders, with a lifetime prevalence of 10.7% (Kessler et al., 2012). Moreover, SAD is the fourth most prevalent of all mental disorders, exceeded only by major depressive disorder, alcohol abuse, and specific phobia (Kessler et al., 2005). This finding is truly remarkable, especially since SAD (previously social phobia) was not included as a separate diagnostic category until the *DSM-III* (APA, 1980).

According to the *DSM-5* (APA, 2013), individuals with SAD fear a number of social and performance situations because of concerns that they will act in a way that will be humiliating or embarrassing or that they will visibly manifest anxiety symptoms (e.g., sweating, shaking, or blushing). For patients with SAD, the fear and avoidance of people typically result in several areas of impairment, including occupational, academic, and social functioning (cf. Heimberg & Magee, 2014). Although the primary characteristics of SAD did not significantly change between the *DSM-IV-TR* (APA, 2000) and the *DSM-5*, the *DSM-5* now includes a *performance-only* subtype, where fear is restricted to speaking or performing in public, and it no longer includes the *generalized* subtype, once defined as fear that is present in most social situations. The median age of onset of SAD is estimated to be 13 years, with 95% of patients reporting onset before age 35 (Kessler et al., 2005). According to Brown and colleagues (2001a), 72% of 186 individuals with a principal diagnosis of SAD seen in a clinic setting also experienced lifetime major comorbid Axis I disorders such as major depressive disorder (44%), dysthymia (17%), alcohol abuse (15%), GAD (14%), drug abuse (11%), obsessive-compulsive disorder (10%), and specific phobia (10%). There is additional evidence that from 25% to 89% of individuals with SAD also meet criteria for avoidant personality disorder (cf. Marques et al., 2012).

Little is known about the etiology of SAD, but numerous studies have examined possible factors, including behavioral inhibition, genetics, biological

mechanisms, developmental factors, conditioning, and cognitive models (Rapee & Spence, 2004). Barlow and colleagues (Barlow, 1988; Barlow et al., 2014a; Barlow, Chorpita, & Turovsky, 1996; Hofmann & Barlow, 2002), invoking the "triple vulnerability" theory again, hypothesize that one must be biologically vulnerable to anxious apprehension to develop SAD and also evidence both general and specific psychological vulnerabilities. If we focus on biological vulnerabilities specifically, there is considerable evidence that genetics plays a role in SAD. In a study of 2,163 female twins, Kendler, Neale, Kessler, Heath, and Eaves (1992) found that proband-wise concordance for SAD was greater in monozygotic (24.4%) than dizygotic (15.3%) twin pairs. This biological vulnerability may express itself in exaggerated reactivity to social evaluation situations. That is, for reasons of evolutionary significance, we are biologically vulnerable to the effects of anger, criticism, and other means of social disapproval. Alternatively, the vulnerability could be a more nonspecific diathesis to experience anxiety generally.

As in all anxiety disorders, a generalized psychological vulnerability also exists in which individuals learn that important, personally salient events in their lives, particularly challenging or threatening events, are unpredictable and uncontrollable (Gallagher, Bentley, & Barlow, 2014). In addition, research suggests that at least some patients with SAD are predisposed to focus anxious apprehension on events involving social evaluation (the specific psychological vulnerability; Barlow et al., 2014a). Anxiety in social evaluative situations involving performance forms the basis from which a false alarm (panic attack) develops in specific social situations. Of course, in some cases, individuals may have direct experience with a traumatic form of social rejection or humiliation, resulting in a true alarm. Another pathway to the acquisition of SAD occurs when socially anxious individuals occasionally experience some performance deficits, even without an encounter with an alarm. Subsequent anxious apprehension in the future may lead to additional performance deficits, which sets off the vicious cycle of anxious apprehension (Hofmann & Barlow, 2002). Although the pathways of acquisition may vary, they have a biological vulnerability, general and specific psychological vulnerabilities, as well as triggering events in common.

Research on CBT for SAD has substantially increased in recent years. The most common approaches include SST, relaxation techniques, exposure-based methods, and multicomponent cognitive-behavioral treatments (e.g., Heimberg & Juster, 1995; Heimberg & Magee, 2014). In this section, as above, empirical studies are evaluated according to the template created by the American Psychological Association to guide the development of practice guidelines described above (APA, 2002; American Psychological Association Task Force on Psychological Intervention Guidelines, 1995 [see Table 14.1]; Barlow & Barlow, 1995). As mentioned in Table 14.1, we have greater confidence in the efficacy of a treatment depending on its absolute and relative efficacy. All studies individually reviewed are type 1 unless otherwise noted.

Social Skills Training

The rationale for SST is based on the concept that people with SAD are deficient in verbal and nonverbal social skills. Heimberg and Juster (1995) pointed out that although social skills deficits were inferred from poor social behavior, the term was often confused with performance deficits. They also concluded that although nine studies used SST as a treatment condition, with some resulting in significant improvement, all but one failed to include appropriate control groups. Therefore, it has not been possible to conclude that training in social skills was the component that led to positive outcomes (Heimberg & Juster, 1995). Similarly, Donahue, Van Hasselt, and Hersen (1994) concluded that the heterogeneity of the samples and the paucity of controlled comparisons have not permitted definitive conclusions on SST's efficacy. Due to the recognized cognitive contributions in the maintenance of social anxiety, as well as the fact that most adults with SAD have adequate social skills, therapy in recent years has targeted cognitive and behavioral interventions for the treatment of this disorder (Ponniah & Hollon, 2008).

Referring to the aforementioned template of treatment efficacy, we cannot definitively state at this time that SST is superior to even a waitlist control because of the methodological limitations in most studies. This conclusion gains credence given that the only controlled study of SST, completed over two decades ago, found that 15 weeks of SST did not result in better clinical outcomes than a waitlist control group (Marzillier, Lambert, & Kelley, 1976). More recently,

another RCT that examined interpersonal therapy with and without SST did not find a significant benefit of SST for those with SAD (Stravynski et al., 2000).

Although SST by itself does not appear to be efficacious, there is some indication that combined SST and exposure holds some promise (Turner, Beidel, Cooley, Woody, & Messer, 1994). In this type 3 pilot study of a comprehensive multicomponent treatment, 11 of 13 patients with severe (generalized) SAD showed moderate to high end-state functioning at posttreatment, although pretreatment status could not be calculated because there were no pretreatment Clinical Global Impression (CGI) ratings; moreover, there was no control group. Another investigation compared the efficacy of cognitive-behavioral group therapy (CBGT) with and without SST (Herbert, Gaudiano, & Rheingold, 2005). The authors found significant improvement in social anxiety symptoms for both groups, although the combined group produced the largest effect sizes. These preliminary findings suggest that additional controlled clinical trials testing this combined treatment are needed. Furthermore, additional dismantling studies must be conducted to explore whether the SST component itself leads to additional improvement above and beyond the gains made from the other components. Obviously, targeting SST specifically to the patients with clearly assessed social skill deficits should produce the most substantial effects.

Relaxation Treatments

The effectiveness of relaxation training and other strategies targeting arousal reduction for social anxiety has not yet been adequately evaluated (Heimberg & Juster, 1995; Heimberg & Magee, 2014). Two groups of investigators have concluded that progressive muscle relaxation alone is not an effective treatment (Al-Kubaisy et al., 1992; Alström, Nordlund, Persson, Harding, & Ljungqvist, 1984). There has been some indication by Öst, Jerremalm, and Johansson (1981) and Jerremalm, Jansson, and Öst (1986a) that applied relaxation, including application training in which relaxation skills are used during anxiety-producing role-plays, is an effective treatment for SAD (cf. Heimberg & Juster, 1995); however, other research suggests that the combination of exposure and applied relaxation does not appear to be superior to cognitive therapy (Clark et al., 2006). In the three controlled clinical trials conducted in this area (Alström et al., 1984; Jerremalm et al., 1986a; Öst et al., 1981), applied relaxation was inferior to self-instruction training, exposure, and supportive counseling and was no better than SST (Donahue et al., 1994). At this time, there is no strong body of literature to support relaxation procedures alone as an effective treatment for SAD.

Exposure and Cognitive Therapy

As we have noted, there is a growing body of literature in support of multifaceted treatment for SAD based on exposure to feared social situations and cognitive therapy (Ponniah & Hollon, 2008). Social anxiety is partially maintained by the avoidance of anxiety-producing situations and the negative reinforcement that occurs as a result (Donahue et al., 1994). Barlow (1988; Hofmann & Barlow, 2002) views some form of exposure as a central part of any psychological treatment for social anxiety; many others would agree. The essential part of exposure is to have a patient repeatedly confront the situation he or she fears. The exposures can be conducted in vivo, with situations encountered in the natural environment or through imaginal exercises. Many treatment programs involve simulated social interactions in which the therapist (and confederates, if necessary) role-play the anxiety-producing social situation. The cognitive component of treatment addresses the role of fear of negative evaluation by identifying and modifying maladaptive cognitions that occur in these situations (Donahue et al., 1994). Although many current treatments for SAD are conducted in a group format (to facilitate exposure), there is also evidence that individual treatment protocols are as, if not more, effective (Mörtberg, Clark, Sundin, & Aberg Wistedt, 2007; Stangier, Heidenreich, Peitz, Lauterbach, & Clark, 2003).

In an early study, Mattick, Peters, and Clarke (1989) randomly assigned 43 patients with SAD to guided exposure alone, cognitive restructuring alone, guided exposure and cognitive restructuring, or a waitlist. All active treatment conditions were significantly better than the waitlist on a behavioral avoidance test, as well as self-report measures of negative evaluation and irrational beliefs. Patients in the combined condition evidenced the most improvement on the behavioral avoidance test. The authors concluded that

exposure therapy combined with cognitive restructuring was the most effective intervention overall.

Heimberg and colleagues (1990) compared a CBGT package, consisting primarily of in-session exposure exercises, cognitive restructuring, and homework exercises, to a credible placebo condition. This placebo condition, called educational supportive group therapy, was a nondirective supportive group treatment that also consisted of psychoeducation about SAD. Both groups improved significantly at posttreatment, but CBGT patients were more improved on some key measures at both posttreatment and at the 6-month follow-up. Moreover, a 5-year follow-up on a portion of the patients from the original study indicated that individuals who received CBGT were more likely to be improved and to maintain their gains relative to the educational support group (Heimberg, Salzman, Halt, & Blendell, 1993). This investigation provides further support for combination treatments involving both exposure and cognitive restructuring.

More recently, Hofmann and colleagues compared the efficacy of CBGT, exposure group therapy, and a waitlist control group for individuals with SAD (Hofmann, 2004; Hofmann, Moscovitch, Kim, & Taylor, 2004). Ninety participants (30 per group) received 12 weekly sessions of group treatment. The CBGT treatment protocol was developed by Heimberg (1991), and the exposure group treatment protocol consisted of repeated in-session in vivo exposures to social situations (including video feedback, didactic training, and weekly homework assignments) and was conducted without explicit cognitive restructuring procedures (Hofmann, 1999). At posttreatment, the two active treatment groups were both significantly better than the waitlist control group, according to two self-report measures of social anxiety and a behavioral stress test, although CBGT and exposure group therapy did not differ from each other. However, at a 6-month follow-up, individuals who received CBGT reported significantly less social anxiety, suggesting that adding cognitive restructuring to an exposure-based treatment protocol may aid in maintaining treatment gains. CBGT has also recently been found to have comparable or superior outcomes to mindfulness-based group treatments for SAD, providing further evidence of its strength as an intervention (Kocovski, Fleming, Hawley, Huta, & Antony, 2013; Koszycki, Benger, Shlik, & Bradwejn, 2007).

Rapee, Gaston, and Abbott (2009) were interested in understanding whether it is important to target factors that may be specific to social anxiety, such as overestimating the likelihood and cost of negative social evaluation, attentional bias toward an excessively negative self-appraisal, and engaging in subtle behavioral strategies that reinforce negative self-perception. They compared standard cognitive restructuring plus in vivo exposure to an "enhanced" program that also included a greater emphasis on hypothesis testing of beliefs through in vivo exposures, obtaining specific performance feedback, and engaging in attention retraining. These two treatments were then also compared to a nonspecific stress management treatment in a sample of 195 individuals with SAD. They found that the enhanced treatment showed the greatest improvements in posttreatment diagnostic severity, anxiety during a speech, although it did not significantly differ from the standard treatment self-report measures of social anxiety symptoms and life impairment. The enhanced condition also showed the greatest improvements on the perceived cost of negative evaluation and negative views of one's skills and appearance, both of which mediated differences between treatments on changes in diagnostic severity. Thus, there is some evidence that providing a more specific treatment tailored to cognitive factors specific to social anxiety may be beneficial.

Clark and colleagues also have examined whether a treatment emphasizing cognitive restructuring could be beneficial to patients with social anxiety, although they did include behavioral experiments, which often contain a significant exposure component. In a sample of 62 individuals with SAD, they compared the efficacy of 14 weekly sessions of individual cognitive therapy to individual exposure treatment plus applied relaxation as well as a waitlist (Clark et al., 2006). The cognitive therapy was based on the model for maintenance of social anxiety developed by Clark and Wells (1995) and included several specific components: (a) developing a personal model of social anxiety for each patient that is consistent with the general model presented; (b) safety behaviors and self-focused attention experiments; (c) shifting focus of attention to the social situation; (d) video feedback; (e) behavioral experiments; (f) identifying problematic anticipatory and postevent processing; and (g) challenging dysfunctional assumptions. Results from the trial showed that cognitive therapy was superior to the individual exposure plus relaxation

on all social anxiety measures at posttreatment and at the 3-month follow-up. At the 1-year follow-up, differences between conditions were less marked, but cognitive therapy continued to outperform individual exposure plus relaxation on most of the social anxiety measures.

In two later randomized trials, Clark's cognitive therapy was compared with interpersonal psychotherapy (Stangier, Schramm, Heidenreich, Berger, & Clark, 2011) and psychodynamic therapy (Leichsenring et al., 2013). CT was found to have superior response rates in comparison to both interpersonal psychotherapy (66% vs. 42%) and psychodynamic therapy (60% vs. 52%) at posttreatment. Taken together, results from these studies suggest that cognitive therapy can have strong outcomes and can outperform waitlist and alternative psychotherapies.

To date, only a small number of studies have compared effective pharmacotherapy treatments to exposure and cognitive therapy elements. In the first published study of this nature, 65 patients with SAD were assigned randomly to one of the four following conditions: CBGT, alprazolam with instructions for self-directed exposure, phenelzine with instructions for self-directed exposure, or placebo with instructions for self-directed exposure (Gelernter et al., 1991). All treatments, including the combination of a placebo plus self-exposure instructions, were associated with substantial improvements in severe and chronic social anxiety, although the results failed to demonstrate definitively the superiority of one treatment over another.

An important multisite (the State University of New York at Albany, Center for Stress and Anxiety Disorders, and the New York State Psychiatric Institute) collaborative project directed by Richard Heimberg and Michael Liebowitz randomly assigned 133 individuals with SAD to one of the following four treatment conditions: CBGT, phenelzine, a psychological placebo (educational supportive group therapy), and a pill placebo (Heimberg et al., 1998). Results indicated that CBGT and phenelzine were equally effective after 12 weeks of treatment, with approximately 60% of patients completing treatment in each group showing substantial improvement. Both were superior to supportive group therapy and pill placebo, which produced improvement rates of approximately 27% and 33%, respectively. After 12 weeks, phenelzine was more effective than CBGT on some self-report measures.

Following the acute phase of the study, responders to this trial entered a 6-month maintenance phase followed by a 6-month treatment-free phase (Liebowitz et al., 1999). No significant differences were detected between the phenelzine patients and CBGT patients during the maintenance phase or the treatment-free phase, although the relapse rate in the phenelzine group (3/14) was higher than in the CBGT group (0/14) at the end of the treatment-free phase.

Another small set of studies have examined whether combination therapy confers additional benefits in comparison to monotherapy. For instance, Clark and colleagues compared cognitive therapy, fluoxetine combined with self-exposure, and placebo combined with self-exposure in patients with generalized SAD (Clark et al., 2003). At posttreatment (16 weeks), results indicated that the results in the patients receiving cognitive therapy were superior to those in patients in other two groups (which did not differ from each other) on all measures of social anxiety. Following the posttreatment assessment, individuals in the placebo-plus-exposure condition were withdrawn from the study, and the remaining patients entered a 3-month booster phase where up to three additional treatment sessions were administered. In addition, patients in the fluoxetine-plus-exposure condition maintained the full dose of fluoxetine. Following the booster session, the cognitive therapy condition was superior to fluoxetine-plus-exposure on five measures of social anxiety. These findings were maintained at the 12-month follow-up, suggesting both the superiority and the durability of cognitive therapy as compared with fluoxetine plus exposure. In addition, the effect sizes for the cognitive therapy condition were double those reported by Heimberg and colleagues (Heimberg et al., 1998).

Another large-scale, multisite RCT compared five treatment conditions for 295 participants diagnosed with SAD: fluoxetine, comprehensive cognitive-behavioral group therapy (CCBT, a modification of CBGT that includes a social skills training component), pill placebo, and their combination (Davidson et al., 2004). Although participants in the fluoxetine condition were significantly improved after 4 weeks (as compared with all other treatment conditions), by the end of 14 weeks there were no significant differences between the four active treatments on measures of social anxiety symptoms, and all active treatments were better than placebo. In addition, response

rates did not differ between the fluoxetine-only group, the CCBT group, the fluoxetine-plus-CCBT group, and the placebo-plus-CCBT group (all significantly better than placebo).

Other more recent RCTs have compared the combination of other medications with CBT. Blanco, Heimberg, and colleagues (2010) compared CBGT, phenelzine sulfate, pill placebo, and CBGT plus phenelzine in a sample of 128 individuals with SAD. After 12 weeks of acute treatment and an additional 12 weeks of intensive continuation treatment, those in the combined treatment and phenelzine groups experienced significantly greater improvements on a number of continuous self-report and clinician-rated measures, with the combined treatment seeing the largest effects. Contrary to prior research (Heimberg et al., 1998), the CBGT group did not exhibit significant differences from the placebo group on continuous measures of symptom severity at 12 weeks. At the end of the continuation phase (at 24 weeks), the combined treatment was still superior, and the two monotherapies performed more similarly. After 24 weeks, 78.1% of the combined treatment group responded (CGI score ≤ 2), compared to 52.9%, 48.6%, and 33.3% of those receiving CBT, phenelzine, or pill placebo respectively.

Similar to the previous discussion of PD treatment, a series of studies conducted in recent years have also examined the benefit of augmenting CBT with DCS for those with SAD (Guastella et al., 2008; Hofmann et al., 2006, 2013). Results from these studies have been mixed: Whereas the two earlier studies by Hofman and Guastella showed a moderate benefit of augmenting CBT with DCS, a larger, multisite RCT conducted by Hofman and colleagues (2013) did not. Hofmann and colleagues randomized 169 individuals with SAD to 12 weeks of CBT augmented with DCS or CBT with pill placebo. While DCS augmentation was associated with a 24% to 33% faster rate of improvement in symptom severity and remission rates, at posttreatment there were no significant differences in response or remission rates between the two conditions.

Based on the empirical research, we can conclude that combined exposure and cognitive therapy treatments are superior to waitlist, nonspecific therapy, and, in some cases, alternative therapies. It is unclear at this point whether the combination of CBT and pharmacotherapy is superior to monotherapy. There is some evidence to suggest the benefit of combination CBT and phenelzine over monotherapy, mixed evidence supporting the augmentation of CBT with DCS, and little evidence suggesting any benefit to combination CBT and fluoxetine.

Psychological Intervention Guidelines

If we return to the psychological intervention guidelines template mentioned above, exposure-based therapies and cognitive therapy are the only treatments for SAD that attain the highest level of treatment efficacy, "better than alternative therapy." Moreover, there is some evidence to support the idea that combining exposure with cognitive restructuring is even more effective than exposure alone (Butler et al., 1984; Hofmann et al., 2004; Mattick & Peters, 1988; Mattick et al., 1989).

Table 14.3 (adapted from Barlow & Lehman, 1996) indicates that combining exposure and cognitive therapy is more effective than exposure alone or educational supportive group psychotherapy in all but one case. In this study (Hope, Heimberg, & Bruch, 1995), CBGT and exposure alone were equally effective, and both were superior to waitlist control. In addition, the four studies involving Clark and Wells' (1995) cognitive therapy indicate superior performance compared to exposure, interpersonal, and psychodynamic therapies. Both Heimberg's CBT and Clark and Wells' cognitive therapy are first-line treatments according to the NICE clinical guidelines (NICE, 2013).

It is less clear whether the combination of psychotherapy and medications is more effective than psychotherapy alone. As we have noted, existing studies that have evaluated the combination of psychotherapy and medications versus psychotherapy alone have produced mixed findings (e.g., Blanco et al., 2010; Davidson et al., 2004; Gelernter et al., 1991; Guastella et al., 2008; Hofmann et al., 2006). Future research will be needed to clarify under what conditions combination treatment is beneficial. For instance, Smits and colleagues (2013) found a moderating effect of in-exposure success for the benefit of augmenting exposure therapy with DCS. In other words, when exposure sessions ended in low fear, individuals who received DCS reported significantly greater improvement at the next session compared to those who received placebo.

TABLE 14.3 Controlled Trials of Psychosocial Treatments for Social Anxiety Disorder

			Significant Comparison (Percentage Clinical Improvement)		
Study	*Length of Follow-Up (Months)*	*Treatment (N)*	*Percentage Clinical Improvement of Completers (If Available)*	*Other Treatments (Yes/No)*	*Waitlist (Yes/No)*
Butler et al. (1984)	6	AMT & E (*N* = 15)		Yes: E	Yes
Mattick and Peters (1988)	3	E & CR (*N* = 11)	86	Yes: E = 52%	Yes
Mattick et al. (1989)	3	E & CR (*N* = 25)		Yes: E	Yes
Heimberg et al. (1990)	6	CBGT (*N* = 20)	81	Yes: ES = 47%	
Heimberg et al. (1993)[a]	54–75	CBGT (*N* = 10)		Yes: ES (most)	
Hope et al. (1995)	6	CBGT (*N* = 13)		No: E	Yes
Gelernter et al. (1991)	2	CBGT (*N* = 20)		No: PH, AL, PL	
Lucas and Telch (1993)	PT	CBGT (*N* = 18)	61	Yes: ES = 24%	
		CBTI	50		
Heimberg et al. (1998)	PT	CBGT (*N* = 28)	75	No: PH = 77%	
				Yes: PL = 41%	
				Yes: ES = 35%	
Liebowitz et al. (1999)[b]	6–12	CBGT (*N* = 14)		Yes: ES = 27%	
				No: PH	
Haug et al. (2003)	6–12	E PL (*N* = 93)		No: E + ST	
				No: ST	
				No: PL	
Clark et al. (2003)	12	CT (*N* = 20)		Yes: FL + SE	
				Yes: PL + SE	
Davidson et al. (2004)		CBGT (*N* = 60)	65	No: CBGT + PL = 60%	
				No: FL = 64%	
				Yes: PL = 40%	
				No: CBGT + FL = 67%	
Hofmann (2004)	6	CBGT (*N* = 30)		No: EGT	
Clark et al. (2006)	12	CT (*N* = 21)	76	Yes: E + AR = 38%	Yes
Hofmann et al. (2006)	1	E + DCS (*N* = 12)		Yes: E + PL	
Koszycki et al. (2007)	PT	CBGT (*N* = 18)		Yes: MBSR	

(continued)

TABLE 14.3 (continued)

			Significant Comparison (Percentage Clinical Improvement)		
Study	*Length of Follow-Up (Months)*	*Treatment (N)*	*Percentage Clinical Improvement of Completers (If Available)*	*Other Treatments (Yes/No)*	*Waitlist (Yes/No)*
Guastella et al. (2008)		E + DCS (*N* = 28)		Yes: E + PL	
Rapee et al. (2009)	PT	E-CBT (N = 71)	42	Yes: CBT = 22%	
				Yes: SM = 10%	
Blanco et al. (2010)	PT	CBGT + PH (*N* = 32)		Yes: PH	
				Yes: PL	
				Yes: CBGT	
Stangier et al. (2011)		CT (*N* = 38)	66	Yes: IPT = 42%	Yes
Hofmann et al. (2013)		E + DSC (*N* = 87)		No: E + DCS	
Leichsenring et al. (2013)		CT (*N* = 209)	60	Yes: PD = 52%	Yes
Kocovski et al. (2013)	3	CBGT (*N* = 32)	44	Yes: MAGT = 43%	Yes

AL = alprazolam; AMT = anxiety management therapy; AR = applied relaxation; CBGT = cognitive-behavioral group treatment; CBTI = cognitive-behavioral treatment—individual; CR = cognitive restructuring; DCS = D-cycloserine; E = exposure; E-CBT = enhanced cognitive-behavioral treatment; EGT = exposure group therapy; ES = educational supportive group psychotherapy (placebo treatment); FL = fluoxetine; IPT = interpersonal psychotherapy; MAGT = mindfulness and acceptance-based group therapy; MBSR = mindfulness-based stress reduction; PD = psychodynamic therapy; PL = pill placebo; PH = phenelzine; PT = posttreatment; SE = self-exposure; SM = stress management; ST = sertraline; WL = wait-list control.

[a]Follow-up study of Heimberg et al. (1990).

[b]Follow-up study of Heimberg et al. (1998).

Adapted from Barlow, D. H., & Lehman, C. (1996). Advances in the psychosocial treatment of anxiety disorders: Implications for national health care. *Archives of General Psychiatry*, 53, 727–735.

In sum, looking at other treatment approaches, at this time we cannot definitively state that SST or relaxation is better than no therapy or in combination with other treatments, like exposure. This is partially due to the methodological limitations of these studies.

Future Directions

While more research is needed to confirm the effectiveness of these treatments, a greater focus on dissemination also is warranted. Along these lines, recent evidence suggests that using a CBT-based therapist guide and corresponding client workbook for SAD can be effective, aiding in dissemination (Goldin et al., 2012; Ledley et al., 2009). In addition, group treatment for SAD can be conducted in an intensive format over a period of 1 to 2 weeks, as opposed to several months, with patients continuing to improve 1 to 5 years after treatment (Mörtberg, Berglund, & Sundin, 2005; Mörtberg, Clark, & Bejerot, 2011). Similar to panic, agoraphobia, and specific phobias, virtual reality is also a possible avenue for increasing the dissemination of treatments for SAD, with some recent evidence suggesting that it can be as effective as standard group therapy (Anderson et al., 2013; Hedman et al., 2011; Klinger et al., 2005). Short-term, intensive treatments or virtual reality treatments would facilitate dissemination by reducing costs and therapist involvement, thus allowing efficacious treatments to be more readily available to clinicians and patients.

GENERALIZED ANXIETY DISORDER

The diagnostic criteria for GAD have undergone substantial modification over the past three decades (Brown, O'Leary, & Barlow, 2001b). In the past, the diagnostic category of GAD, first formulated in 1980 (APA, 1980), resulted in enormous confusion (Barlow, 1988, 2002; Barlow & Wincze, 1998). This was partly due to its residual status, which meant that the diagnosis of GAD could not be assigned if a person met criteria for any other mental disorder (Brown et al., 2001b). This convention was based on the notion that generalized anxiety was an integral part of many disorders and therefore could not be easily separated from the general clinical presentation. In the *DSM-III-R* (APA, 1987), for the first time key defining features (e.g., excessive worry and persistent somatic concerns) were presented that elevated GAD beyond a strictly residual category (Brown et al., 2001b). These criteria were further delineated and sharpened by the *DSM-IV* and *DSM-IV-TR* (APA, 1994, 2000), as the number of associated physical symptoms associated with worry was reduced and the lack of control over worry was highlighted as a diagnostic feature. The diagnostic criteria for the *DSM-5* have not changed from *DSM-IV*, and recent estimates suggest the lifetime prevalence of GAD to be 6.2% (APA, 2013; Kessler et al., 2012).

As a result of changes in the diagnostic criteria and new data on prevalence, the number of research studies on important characteristics of GAD, as well as empirical treatment outcome studies, has increased in recent years. However, given that GAD may be the "basic" anxiety disorder in the sense that generalized anxiety is a consistent component of other anxiety disorders (with the possible exception of specific phobia), treatments for GAD have received surprisingly little attention (Barlow, 1988, 2002; Brown et al., 2001b). In fact, Dugas and colleagues have consistently found that GAD is one of the least studied anxiety disorders over the past 20 years, second only to specific phobias (Dugas, 2000; Dugas, Anderson, Deschenes, & Donegan, 2010). However, of the relatively small number of publications focused on GAD, approximately 44% have been on treatment research in the past 15 years (Dugas et al., 2010).

Our model (Barlow, 1988, 2000, 2002) of the etiology of GAD suggests that biological and psychological vulnerabilities line up to create a diathesis for chronic anxiety. Stress-related negative life events trigger neurobiological reactions such as increased corticotropin-releasing factor, chronic activation of the hypothalamic-pituitary-adrenocortical axis, and the sense that events are proceeding in an uncontrollable and unpredictable way. The focus of attention is shifted from the task at hand to a maladaptive self-evaluative mode, which further increases arousal. This results in increased vigilance and the narrowing of attention to the threat or challenge. This arousal-driven cognitive process continues to escalate in a negative feedback loop, resulting occasionally in performance disruption, attempts to cope, including situational avoidance, if possible, and/or a maladaptive worry process that seems to serve as a method of avoiding core negative affect (Barlow, 2000, 2002; Borkovec, 1994; Craske, 1999).

Until recently, clinical outcome studies have demonstrated only modest treatment gains for GAD compared to treatment gains with other anxiety disorders. These less satisfying results have been hypothesized to result from, among other things, the high rates of comorbidity found in patients with GAD and the fact that GAD tends to be chronic, as patients often recall a lifelong history of the disorder (cf. Brown et al., 2001a).

Given the vagueness of earlier criteria, initial studies on the treatment of GAD used nonspecific treatment approaches such as relaxation or biofeedback. It has only been in the past two decades, since the *DSM-IV* was introduced, that more rigorous controlled trials of treatment for GAD have been conducted, using more specific treatment techniques such as cognitive and behavior therapy as well as combinations of several treatment components aimed at targeting the key features of the disorder.

To properly evaluate the question of treatment choice, one must consider both the efficacy of the treatment and the clinical utility of that technique. In this section, as above, the treatment techniques reviewed focus on treatment efficacy. However, because there are fewer treatment outcome studies for GAD (relative to the other disorders reviewed in this chapter) and because many studies test multiple active treatments, this section is organized in three categories of increasing confidence in treatment efficacy: (a) better than no therapy (RCTs), (b) better than nonspecific therapy (RCTs), and (c) better than alternative therapy (RCTs).

Better than No Therapy

Some researchers have found that active treatment is preferable to no therapy but that different active treatments may not exhibit differential efficacy. In a study conducted in our center (Barlow, Rapee, & Brown, 1992), 65 patients meeting the *DSM-III-R* criteria for GAD were randomized to one of four treatment groups: applied progressive muscle relaxation, cognitive restructuring, a combination of relaxation and cognitive restructuring, or a waitlist control. All patients in the active treatment conditions received 15 hour-long sessions. Treated patients were significantly better compared with those in the waitlist control group. However, as stated above, differential efficacy was not found among active treatment components. Moreover, differential dropout rates were encountered among the active treatments (8% in the combination group to 38% in the relaxation group).

More recently, two separate studies have been conducted comparing a new CBT for GAD compared with a waitlist control group (Dugas et al., 2003; Ladouceur et al., 2000). Based on recent research suggesting the role of intolerance of uncertainty in GAD, the authors used a treatment protocol that specifically targets worry (e.g., components are aimed to target four aspects of GAD: intolerance of uncertainty, erroneous beliefs about worry, poor problem orientation, and cognitive avoidance). In the first trial using an individual treatment protocol, 26 patients were included (14 received immediate treatment, 12 were assigned to a delayed-treatment waitlist control). Results indicated that, compared to the waitlist control, patients in the treatment condition showed greater improvements on outcome measures that were maintained through the 1-year follow-up (Ladouceur et al., 2000). Additionally, 77% no longer met criteria for GAD following treatment. In the second trial, which included treatment components of awareness training (i.e., learning to be aware of worries) and cognitive exposure (i.e., each patient recorded a "worst fear" on an audiotape and listened to the recording daily, until the scenario no longer provoked anxiety), 52 GAD patients received 14 sessions of group therapy for their symptoms (Dugas et al., 2003). Of these, 25 received immediate treatment and 27 were assigned to a delayed-treatment control condition. At posttreatment, treated patients demonstrated significant improvement on all measures compared with waitlist patients, and results were maintained through the 24-month follow-up. The authors suggest that group CBT may be a viable and less costly option for individuals with GAD (Dugas et al., 2003).

Another newer treatment approach for GAD draws from traditional components of CBT, including psychoeducation, monitoring, and relaxation exercises, as well as strategies from other therapies such as Acceptance and Commitment Therapy (ACT; Hayes, Strosahl, & Wilson, 2011), Dialectical Behavior Therapy (DBT; Linehan, 1993), and MBCT (Segal, Williams, & Teasdale, 2002). The new treatment, Acceptance-Based Behavior Therapy (ABBT) for GAD, encourages acceptance and awareness of worry, rather than thought challenging, and mindful action as an alternative to the habitual inaction that often results from the worry associated with GAD (Orsillo, Roemer, & Barlow, 2003). A small-scale RCT comparing ABBT and delayed treatment in 31 individuals with GAD found that ABBT was associated with greater improvements in GAD severity, worry, and depressive symptoms at posttreatment that were maintained through the 3- and 9-month follow-up periods (Roemer, Orsillo, & Salters-Pedneault, 2008). At posttreatment, 75% of participants treated with ABBT were categorized as responders to treatment versus 8.3% of those in the delayed-treatment condition.

Better than Nonspecific Therapy

Several controlled clinical trials have found that a specific treatment for GAD is better than nondirective treatment (Borkovec & Costello, 1993; Borkovec et al., 1987; Gosselin, Ladouceur, Morin, Dugas, & Baillargeon, 2006). In an early study (Borkovec et al., 1987), 30 patients who met the *DSM-III* criteria for GAD were randomly assigned to one of two groups: progressive muscle relaxation with cognitive therapy or progressive muscle relaxation with nondirective therapy. Overall, all patients improved substantially by the end of treatment and also at the 6-to 12-month follow-up, as shown by clinician ratings, self-report questionnaires, and daily self-monitoring. However, the group receiving cognitive therapy was superior to the group receiving nondirective therapy on all but one posttreatment outcome measure. In addition, patients receiving cognitive therapy attributed more of their improvement to the cognitive component of treatment than patients receiving nondirective therapy did to the general psychotherapy

they received. The authors concluded that cognitive therapy contains an active ingredient above and beyond the nonspecific psychotherapy treatment factors.

Similar results were found when Gosselin and colleagues (2006) examined whether CBT facilitated a benzodiazepine tapering program. Sixty-one patients with GAD were randomized to undergo a 12-week gradual medication discontinuation protocol combined with either CBT or a nonspecific psychological treatment. Patients who received CBT were approximately twice as likely to discontinue benzodiazepines than the nonspecific treatment group (74% vs. 37%) at posttreatment, and results were maintained over a year-long follow-up period. Patients who underwent CBT were also more likely to no longer meet criteria for GAD at posttreatment (36% vs. 80%).

Better than Alternative Therapy

A final group of studies has been conducted that compares at least two efficacious psychotherapy treatments to each other. According to the template, demonstrated efficacy in this category results in the highest level of confidence in a given treatment. Although most investigations of this type have not resulted in significant differences emerging among active treatments (Barlow et al., 1992; Blowers et al., 1987; Borkovec & Mathews, 1988; Durham & Turvey, 1987; Hayes-Skelton et al., 2013; White & Keenan, 1992), a few empirical studies have demonstrated the superiority of one active treatment over another (Butler, Fennell, Robson, & Gelder, 1991; Dugas et al., 2010; Durham et al., 1994; Wells et al., 2010).

In an empirical investigation, 57 patients meeting the *DSM-III-R* criteria for GAD were randomly assigned to one of three treatment groups: CBT, behavior therapy, or a waitlist control group (Butler et al., 1991). In this controlled clinical trial, independent assessments were conducted before treatment, at the end of treatment, at a 6 month follow-up, and at an 18 month follow-up. Treatment lasted for up to 12 sessions; patients and their therapists could agree to conclude treatment after a minimum of 4 sessions if the patients' anxiety levels were low and stable. The behavior therapy package consisted of progressive muscle relaxation, reducing avoidance through graduated exposure, and building confidence by reinitiating pleasurable activities. The rationale for behavior therapy was that anxiety is maintained by avoidance of anxiety-producing situations, the person's reaction to the symptoms, and loss of confidence. The CBT package consisted of cognitive therapy as described by Beck and Emery (1985), as well as behavioral assignments. The rationale for CBT treatment was that anxiety is maintained by anxious thoughts and lack of self-confidence, which can be controlled by recognizing anxious thoughts, seeking helpful alternatives, and taking action to test these alternatives. Results showed a superiority of CBT over behavior therapy, as demonstrated through measures of anxiety, depression, and cognition. However, the patients in the behavior therapy group had improved significantly on all but one measure of anxiety and maintained their gains 6 months later.

As noted in an earlier section, Borkovec and Costello (1993) compared the efficacy of CBT, applied relaxation, and nondirective treatment in a sample of 55 patients who met the *DSM-III-R* criteria for GAD. For this study, patients in the nondirective treatment condition were told that the goals of treatment were to enhance self-understanding and to discover things they could do differently to affect how they feel. All three treatments were reported to be highly credible to the patients. The relaxation and CBT treatment conditions did not differ significantly from each other but were both superior to ND at posttreatment. However, during a 1-year follow-up, 57.9% of patients receiving CBT met a high end-state functioning criterion (meaning they were close to "cured"), whereas only 33.3% of patients in the relaxation group and 22.2% of patients receiving nondirective therapy met this criterion.

Additional research has also suggested that a comprehensive CBT package is not necessarily more efficacious than the individual protocol components. Borkovec, Newman, Pincus, and Lytle (2002) compared three treatments for GAD: (a) applied relaxation training combined with self-control desensitization, (b) cognitive therapy, and (c) their combination (CBT). Contrary to expectations, there were no significant differences among the three groups on self-report or clinician-rated measures, suggesting that applied relaxation, self-control desensitization, and cognitive therapy are not necessarily more efficacious when used in combination.

In comparisons of CBT approaches to pharmacological treatment, CBT has also been shown to be superior to benzodiazepines in several controlled

clinical trials (Lindsay, Gamsu, McLaughlin, Hood, & Espie, 1987; Power et al., 1990; Power, Jerrom, Simpson, Mitchell, & Swanson, 1989). In one study (Power et al., 1990), 101 patients meeting the *DSM-III* criteria for GAD were randomly assigned to one of the following 10-week treatment conditions: CBT, diazepam, placebo, CBT plus diazepam, or CBT plus placebo. Posttreatment and 6-month follow-up measures indicated the superiority of all CBT treatments, especially CBT alone and the CBT-plus-diazepam combination. For more information on psychopharmacological treatments of GAD, please refer to Chapter 13.

More recently, three newer forms of CBT have been compared to an alternative treatment (applied relaxation) in a series of controlled trials (Dugas et al., 2010; Hayes-Skelton, Roemer, and Orsillo, 2013; Wells et al., 2010). Dugas and colleagues (2010) compared their form of CBT, which targets intolerance of uncertainty, to relaxation and a delayed-treatment waitlist condition in a sample of 65 adults with GAD. Participants completed 12 weeks of CBT or relaxation training and were followed for 24 months. At posttreatment, they found CBT was superior to waitlist on overall GAD severity as assessed by clinician severity ratings and measures of pathological worry, somatic symptoms of GAD, and global clinical improvement. Relaxation was only superior to waitlist on overall severity of GAD. CBT was superior to relaxation on global clinical improvement but not other measures. However, the CBT condition was associated with significant improvements in worry, trait anxiety, and global clinical improvement over the 2-year follow-up period, whereas the relaxation condition was not, suggesting some additional benefit of CBT over relaxation training.

Metacognitive therapy, yet another new form of CBT, consists of 8 to 12 weekly individual sessions and focuses on modifying erroneous negative metacognitive beliefs, positive metacognitive beliefs, and unhelpful thought-control strategies (Wells & King, 2006). This therapy is based on the idea that metacognitive processes involved in worry are particularly important to the development of GAD, specifically beliefs about the dangerousness and uncontrollability of worry (Wells, 1995). A small RCT comparing metacognitive therapy and applied relaxation (N = 20; Wells et al., 2010) found that 80% of individuals with GAD who participated in metacognitive therapy recovered versus 10% of participants in the relaxation group. Recovery was defined using trait anxiety scores, although significant improvements were found in worry and depression as well. Participants who underwent metacognitive training maintained their recovery status over a 6- and 12-month follow-up and continued to outperform the relaxation group over time (70% recovery rate for the metacognitive group at 6 and 12 months vs. 20% for the relaxation group at both follow-up assessments). However, while these results are promising, the small sample size and low rates of response to applied relaxation indicate a need to confirm the findings from this RCT.

Taking this literature a step further, van der Heiden, Muris, and van der Molen (2012) recently conducted an RCT comparing metacognitive therapy and Dugas and colleagues' version of CBT, referred to here as Intolerance of Uncertainty Therapy (IUT; Dugas et al., 2003). The sample included 126 patients diagnosed with GAD who were randomized to metacognitive therapy, IUT, or a delayed-treatment condition. The active treatment conditions consisted of up to 14 weeks of individual sessions, and participants completed assessments before treatment, at the end of treatment, and at a 6-month follow-up. Both metacognitive therapy and IUT outperformed delayed treatment on reductions in worry, trait anxiety, and depressive symptoms, as well as the percentage of clients no longer meeting diagnostic criteria for GAD at posttreatment (metacognitive therapy, 93%; IUT, 80%; delayed treatment 5%). Improvements were maintained at the 6-month follow-up. When examining the intent-to-treat sample, patients in the metacognitive therapy condition exhibited significantly greater reductions in worry, depressive symptoms, and trait anxiety than the IUT group, although differences were less pronounced when examining the subset of the sample who completed treatment.

Although promising results were found with both treatment conditions and some suggested additional benefit of metacognitive therapy over IUT, further research is needed to have a better understanding of the comparative effects of these treatments. Van der Heiden and his colleagues noted the performance of IUT may not have been fully representative in this trial, as they made some changes to the protocol and the developers of IUT themselves made a change to the protocol while the study was being conducted (Dugas & Robichaud, 2007). In this trial, reevaluation of positive beliefs about worry was moved to later in the protocol and patients engaged in exposure

to worry images not conducive to problem solving instead of listening to recordings of the worry images on a looped tape. While this study was under way, Dugas and colleagues added uncertainty recognition and behavioral exposures to their treatment.

Finally, Hayes-Skelton and colleagues (2013) very recently conducted a well-done RCT comparing ABBT and applied relaxation in a sample of 81 individuals with GAD. Patients in both treatment conditions received 16 sessions of treatment and were followed for 6 months after treatment. Unlike the results found by Dugas and colleagues (2010) and Wells and colleagues (2010), ABBT and relaxation exhibited comparably strong outcomes at posttreatment, with 70.0% of those in the ABBT group being classified as responders to treatment in comparison with 78.8% of those in the relaxation group. At a 6- month follow-up, the treatment gains were maintained: 76.0% of the ABBT individuals were classified as responders versus 71.4% of those in the relaxation group. However, the relaxation training performed particularly strongly in this trial compared to what was observed by Wells and colleagues (2010).

Translational Research (Effectiveness Studies)

Surveys reveal that people with anxiety difficulties are prevalent in primary care settings, suggesting a need for the development of brief, cost-effective treatments (Barlow, Lerner, & Esler, 1996). Along these lines, Rollman and colleagues (2005) compared the effectiveness of a telephone-based managed care intervention with treatment as usual for 191 patients diagnosed with either PD or GAD (although 90% of the full sample carried a GAD diagnosis). Patients were randomly assigned to one of the two interventions. Those assigned to the telephone-based managed care condition were offered any combination of three intervention components: (a) a workbook designed to assist with self-management of anxiety with follow-up contact from a care manager (Craske, Barlow, & O'Leary, 1992), (b) a trial of pharmacotherapy, or (c) a referral to a community mental health care provider. Of note, the vast majority of patients (80%) chose the self-management workbook. At the 12-month follow-up, although the intervention was less successful in reducing anxiety symptoms for patients with GAD only as compared to PD, all patients who received an intervention showed significant improvements in anxiety symptoms, quality of life, the number of hours worked, and the number of days absent from work compared with those who received usual care. These data suggest that treatment in a primary care setting is not only feasible and acceptable to patients with GAD but also successful in reducing symptoms that may lead to reductions in health care costs. In an era of rising health care costs, developing brief, cost-effective, and perhaps self-directed treatments with proven efficacy for the treatment of GAD in primary care offices will be an important step for future research in the area.

Future Directions

The more we learn about the nature of GAD, the more we should be able to improve our psychotherapeutic treatments. Additional dismantling studies should assist in determining the specific mechanisms of action in successful therapy. At this time, CBT approaches are one of the most widely evaluated types of psychotherapy for GAD. In fact, a recent meta-analysis by Hanrahan, Field, Jones, and Davey (2013) found CBT was superior to nontherapy controls (d = 1.81) and non-CBT therapy (d = .63). The magnitude of effect for recent studies comparing CBT to non-CBT treatments was larger than previously found, possibly suggesting increased efficacy of newer forms of CBT. The results of studies comparing CBT to other treatments or a waitlist are summarized in Table 14.4 (adapted and updated from Barlow & Lehman, 1996).

Until recently, most studies have not demonstrated differential rates of efficacy for active treatment techniques. However, most studies have shown that active treatments are superior to nondirective approaches and uniformly superior to no treatment. Hence, the most recent NICE (2011) guidelines recommend both CBT and applied relaxation as treatment options if less intense treatments such as self-help or psychoeducational groups are not beneficial. Although more research in this area is warranted, substantial progress is evident during the past decade, particularly in the past several years. Promising new CBT approaches, such as ABBT, metacognitive therapy, and Dugas and colleagues' CBT focusing on intolerance of uncertainty, have been shown to be superior or equivalent to other active treatments (Dugas et al., 2010; Hayes-Skelton et al., 2013; Wells et al., 2010). Future

TABLE 14.4 Controlled Trials of Cognitive-Behavioral Treatments for Generalized Anxiety Disorder

Study	Length of Follow-Up (Months)	Treatment (N)	Percentage Clinical Improvement of Completers (If Available)	Significant Comparison (Percentage Clinical Improvement)	
				Other Treatments (Yes/No)	Waitlist (Yes/No)
Barlow, Cohen et al. (1984)	6	CBT (*N* = 5)			Yes
Blowers et al. (1987)	6	CBT (*N* = 20)		Yes: ND (some measures)	Yes
Borkovec et al. (1987)	6–12	CT PR (*N* = 16)		Yes: ND + PR (some measures)	
Butler et al. (1987)	6	CBT (*N* = 22)	58.5		Yes (0%)
Borkovec and Mathews (1988)	12	CT PR (*N* = 6)		No: SCD + PR	No: N + PR
Power et al. (1989)	PT	CBT (*N* = 10)		Yes: PL (one central measure) No: DZ (one central measure)	
Power et al. (1990)	PT	CBT (*N* = 21)	61.9	No: CBT + DZ = 69.8% No: CBT + PL = 55.6% Yes: DZ = 30.3% Yes: PL = 17.5%	
Butler et al. (1991)	6	CBT (*N* = 18)	42	Yes: BT = 5%	Yes
Barlow et al. (1992)	6	CBT (*N* = 29)	55		Yes
White and Keenan (1992)	6	CBT (*N* = 26)		No: BT, CT	Yes Yes
Borkovec and Costello (1993)	12	CBT (*N* = 18)	57.9	Yes: ND = 26.7% Yes: AR = 37.5%	
Durham et al. (1994)[a]	6	CT (*N* = 40)	> 60	Yes: AP < 31% Yes: AMT < 37%	
Ladouceur et al. (2000)	6–12	CBT (*N* = 14)	54		Yes
Borkovec et al. (2002)	6–24	CT (*N* = 23)	52	No: CBT = 38% No: AR + SCD = 48%	
Arntz (2003)	6	CT (*N* = 25)	50	No: AR = 46%	
Dugas et al. (2003)	6–24	CBT-G (*N* = 25)	62		Yes
Rollman et al. (2005)[b]	12	I (*N* = 116)		Yes: UC	
Roemer et al. (2008)		ABBT(*N* = 15)	75		Yes
Wells et al. (2010)	12	MCT(*N* = 10)	80	Yes: AR = 10%	
Dugas et al. (2010	24	CBT (*N* = 23)	70	No: AR = 55%	

(continued)

TABLE 14.3 (continued)

Study	Length of Follow-Up (Months)	Treatment (N)	Percentage Clinical Improvement of Completers (If Available)	Significant Comparison (Percentage Clinical Improvement)	
				Other Treatments (Yes/No)	Waitlist (Yes/No)
Hayes-Skelton et al. (2013)	6	ABBT(N = 40)	70	No: AR = 79%	
van der Heiden et al. (2012)		MCT(N = 61)	77	Yes: CBT = 63%	Yes

ABBT = acceptance-based behavioral therapy; AMT = anxiety management training; AP = analytic psychotherapy; APL = attention placebo; AR = applied relaxation; BT = behavior therapy; CBT = cognitive-behavioral therapy; CBT-G = cognitive-behavioral therapy-group format; CT = cognitive therapy; DZ = diazepam; FU = follow-up; I = intervention (either self-management workbook, trial of pharmacotherapy, or referral to mental health care provider); MCT = metacognitive therapy; ND = nondirective therapy; PL = pill placebo; PR = progressive relaxation; PT = posttreatment; SCD = self-control desensitization; UC = usual care.

[a]Intent-to-treat.

[b]Study comparison included patients with diagnosis of GAD, although it was not designated whether GAD was assigned as principal.

Compiled and adapted from Barlow, D. H., & Lehman, C. (1996). Advances in the psychosocial treatment of anxiety disorders: Implications for national health care. *Archives of General Psychiatry*, 53, 727–735; and Borkovec, T. D., & Whisman, M. A. (1996). Psychosocial treatment for generalized anxiety disorder. In M. Mavissakalian & R. Prien (Eds.), *Long-term treatments of anxiety disorders* (pp. 171–199). Washington, DC: American Psychiatric Press.

research will need to be conducted to further establish the efficacy of these recently developed interventions and to explore whether any of these treatments perform consistently better than other CBT approaches for GAD. Also important will be analyses of how these treatments may have similar core components and mechanisms of action. In addition, more research needs to be conducted examining the effectiveness of treatments for GAD in primary care and community settings.

TRANSDIAGNOSTIC TREATMENT

Thus far, we have reviewed a number of CBT approaches that have been developed and rigorously evaluated for PD, agoraphobia, specific phobia, SAD, and GAD. Although these interventions have shown efficacy (and, for some, effectiveness) in treating these disorders, limitations posed by the proliferation of these diagnosis-specific treatments have been increasingly acknowledged in recent years. One criticism of these approaches is the reliance on multiple manuals and clinicians skilled in delivering the protocols in all of these manuals. Thus, the development of these often complex protocols has resulted in problems with dissemination and a paucity of adequately trained professionals. Research conducted over the past several decades has also resulted in strong evidence for considerable overlap among the anxiety and mood disorders (e.g., Barlow, 2004; Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2014b; Moses & Barlow, 2006), which may be explained by shared underlying commonalities (e.g., increased emotional reactivity, attempts to alter or avoid emotional responding; Barlow, 2002; Brown, 2007; Brown & Barlow, 2009). There is also research suggesting that CBT for one anxiety disorder often leads to simultaneous improvement in co-occurring conditions (e.g., Borkovec, Abel, & Newman, 1995; Brown & Barlow, 1995; Craske et al., 2007), although effects may not be durable for nontargeted disorders (Brown & Barlow, 1995). Collectively, these areas of research have set the stage for more parsimonious approaches to treating the anxiety disorders.

To meet this need, several programs containing core CBT strategies used to treat all anxiety and related disorders (transdiagnostic) have been developed and tested (e.g., Barlow, Allen, & Choate, 2004; Norton, 2008). One such intervention that has garnered the interest of researchers and clinicians alike is the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP; Barlow et al., 2011a, 2011b; Payne, Ellard, Farchione, Fairholme, & Barlow, 2014). Briefly, the major components of this treatment involve fostering present-focused,

nonjudgmental emotion awareness, altering cognitive reappraisals, preventing emotional avoidance, increasing tolerance of physical sensations associated with anxiety and distress, and facilitating action tendencies not associated with dysregulated emotions (Payne et al., 2014; Wilamowska et al., 2010). Some treatment components are almost identical to those commonly employed in evidence-based CBT protocols for specific anxiety disorders; however, the UP modules are designed to be applicable across anxiety and mood disorders, as well as other disorders characterized by intense negative and dysregulated emotions (e.g., somatic symptom disorders). The UP also extends traditional CBT strategies by including a more explicit focus on the interaction of thoughts, feelings, and behaviors, emphasizing the functional nature of emotions, and encouraging greater tolerance of emotions (Ellard et al., 2010).

The UP has been subjected to empirical testing in a number of trials to date. In the first (type 2) pilot study, 18 diagnostically heterogeneous participants began a 15-session course of individual treatment (Ellard et al., 2010). This trial used an earlier version of the protocol, which comprised psychoeducation about emotions, alteration of antecedent cognitive misappraisals, prevention of emotion avoidance, and modification of emotion-driven behaviors (Allen, McHugh, & Barlow, 2008). Principal diagnoses included PD with agoraphobia, SAD, GAD, obsessive-compulsive disorder, posttraumatic stress disorder, major depressive disorder, and hypochondriasis. Results showed significant, yet modest, pretreatment-to-posttreatment effects across principal and comorbid disorders, suggesting that there was a need for continued development and refinement of the treatment manual. After making further modifications to the protocol (e.g., increasing emphasis on present-focused, nonjudgmental emotion awareness), a second open trial of the UP was conducted in a sample of 15 similarly diagnostically heterogeneous patients (Ellard et al., 2010). Findings showed that 73% of patients met responder status, and 60% achieved high end-state functioning for their principal disorder(s). With regard to comorbid disorders, 64% of patients attained both responder status and high end-state functioning. At the 6-month follow-up, results were even more promising, with 85% of patients achieving responder status on their principal diagnosis and 69% meeting criteria for high end-state functioning. In terms of comorbid disorders, 80% of patients achieved responder status, and 50% of the total sample attained high end-state functioning at follow-up.

More recently, the first RCT of the UP was conducted. Farchione and colleagues (2012) randomly assigned 37 patients with a principal anxiety disorder (PD with agoraphobia, SAD, GAD, obsessive-compulsive disorder, anxiety disorder not otherwise specified, and/or posttraumatic stress disorder) to receive 16 sessions of the UP (n = 26) or a waitlist control condition (n = 11). The protocol used in this trial followed that employed in the second pilot study by Ellard and colleagues (2010), with the addition of a motivational enhancement module and greater emphasis on increasing positive emotions (Barlow et al., 2011a; Payne et al., 2014). At posttreatment, 50% of patients in the UP condition met subclinical status (and achieved high end-state functioning) on their principal diagnoses (vs. 0% of the waitlist) and 45% of UP patients no longer met criteria for any clinical diagnoses (vs. 0% of the waitlist). Also at posttreatment, 50% of patients in the UP condition no longer met criteria for any comorbid diagnoses (vs. 17% of the waitlist; this difference did not reach statistical significance). Individuals with different principal anxiety disorder diagnoses who received the UP responded similarly, with all but one effect size estimate for diagnosis-specific measures in the very large range at the end of treatment and at the 6-month follow-up. The UP also showed strong response rates at the follow-up assessment, with 71% of UP patients achieving subclinical status on their principal diagnosis and 64% on all clinical diagnoses.

Taken together, findings from these initial studies provide preliminary support for the efficacy of UP as a transdiagnostic treatment for anxiety disorders, including those reviewed in this chapter. Results also show that the UP has moderate to large effects on measures of negative and positive affectivity, which is consistent with the treatment's overall emphasis on affective processing. A large-scale noninferiority study is under way at our center in Boston to examine the efficacy of the UP in comparison to established single-diagnosis CBT protocols. This initiative, and other upcoming work to identify the specific mechanisms by which the UP obtains its effects, has the potential to establish the UP as a more efficient, and perhaps more effective, approach to the treatment of anxiety and related disorders than "gold-standard" single-disorder treatments.

Similarly promising results have been observed for other transdiagnostic treatments. For example, in 2012, Norton and Barrera published findings from a type 1 trial comparing the efficacy of a transdiagnostic CBT group protocol to diagnosis-specific CBT protocols. Patients (N = 46) with a principal diagnosis of PD, SAD, or GAD were randomly assigned to 12 weekly 2-hour group sessions of the transdiagnostic or diagnosis-specific treatment. Session-by-session analyses indicated that transdiagnostic CBT had noninferior outcomes in comparison to diagnosis-specific CBT. At posttreatment, no significant differences between conditions were observed; for instance, the percentage of patients classified as responders in the transdiagnostic versus diagnosis-specific condition (64.7% vs. 69.2%, respectively) was similar. In addition to studies that include a control condition and employ larger, more diverse samples and follow-up assessments, future research should aim to determine whether this and other transdiagnostic interventions (e.g., Barlow et al., 2011) facilitate significant advances in dissemination and training.

Transdiagnostic treatments for anxiety disorders can also be offered through Internet sources. This approach may be particularly well suited to reducing barriers to dissemination, as the advantages of transdiagnostic strategies are combined with increased accessibility and convenience for patients and clinicians, as well as ensured treatment fidelity (Andrews et al., 2010). To date, several electronic or Internet-based transdiagnostic interventions have been developed and evaluated, including the Coordinated Anxiety Learning and Management (CALM) intervention (Craske et al., 2011) and the Wellbeing Program (Titov et al., 2011). Generally, studies in this area provide support for the efficacy of transdiagnostic computerized CBT, thereby suggesting the potential of this innovative approach (e.g., Dear et al., 2011; Roy-Byrne et al., 2010).

For example, one recent, large-scale study examined the effectiveness of an evidence-based intervention comprising CBT and/or pharmacotherapy recommendations compared to usual care in 17 primary care clinics (Craske et al., 2011). The CALM intervention is a computer-assisted CBT program that addresses the four most common anxiety disorders in primary care settings (panic, GAD, SAD, and posttraumatic stress disorder). CALM contains eight modules; cognitive restructuring and exposure modules are tailored to each of the four anxiety disorders through branching systems, whereas the other modules are mostly generic (Craske et al., 2009). In this trial, 1,004 patients meeting diagnostic criteria for a principal anxiety disorder (262 with panic, 132 with SAD, 549 with GAD, and 61 with posttraumatic stress disorder) were randomly assigned to receive CALM or usual care for up to 12 months. Those randomized to CALM could select a combination of CBT and medication management, or medication management only; between 46% and 65% of patients (depending on principal diagnosis) in the intervention condition chose CBT plus medication, while only 9% chose medication alone. At 6 months, CALM was superior to usual care in reducing symptoms of GAD, SAD, and panic, as well as showing higher response rates for GAD and SAD. At 12 months, CALM was also superior to usual care in remission rates for PD. For comorbid disorders, effect sizes favored the intervention, but there were no statistically significant differences. These findings suggest that providers with little or no training in mental health can deliver effective CBT treatment with the aid of a computerized guide, combined with medication recommendations, to diverse patient populations in primary care settings. These data also indicate that computer-assisted, transdiagnostic CBT can affect not only general outcome measures of anxiety but also disorder-specific outcomes.

Given the significant implications for dissemination and training posed by computer-based, transdiagnostic treatments, key unanswered questions for future research include the optimal length of these programs, the ideal balance of clinician contact, the most important treatment elements, and the relative short- and long-term efficacy and cost-effectiveness compared to disorder-specific approaches. Combining Internet-based, modular formats (e.g., Carlbring et al., 2011) with a transdiagnostic approach may also represent an important area for future work in this area, as individually tailored treatment may prove more acceptable, efficient, and/or efficacious than one-size-fits-all methods.

CONCLUSIONS

It is clear that a multitude of efficacious psychological treatments for a variety of anxiety disorders exist; however, there is still considerable room for continued testing and refinement. For one, we are only

beginning to explore the effectiveness of these procedures outside of research trials. In addition to questions about the generality of effectiveness across patients, settings, and therapists of differing skills and abilities, criticisms have also been raised about the feasibility of these treatments, as well as their cost-effectiveness. Many of these issues are outlined succinctly in the template for psychological intervention guidelines referred to above (APA, 2002; American Psychological Association Task Force on Psychological Intervention Guidelines, 1995), which provides a road map for future research. Emerging findings suggest that many of these procedures are just as effective or more effective when applied in a variety of practice settings as they are in the clinical research settings where they were developed (Barlow, 1996; Barlow & Barlow, 1995), but further research in this area is necessary.

As we have emphasized, we must improve efforts to disseminate these treatments to the variety of practice settings in which they should prove useful, many of them primary care settings, to meet the demands of many patients with these disorders who desire brief, effective treatment. Evidence indicates that effective psychological treatments are much less readily available than pharmacological interventions in most settings and are often suboptimally delivered (Barlow, Levitt, & Bufka, 1999; Craske et al., 2011). Thus, it is not enough simply to develop these treatments and report on their efficacy or effectiveness. Rather, it is the responsibility of those involved in treatment development to continue evaluating methods of training and dissemination, such as those that incorporate innovative technologies and/or transdiagnostic approaches applicable across diverse patient presentations, to ensure that these treatments reach the greatest number of people who need them.

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15

Pharmacological Treatments for Panic Disorder, Generalized Anxiety Disorder, Specific Phobia, and Social Anxiety Disorder

Ryan J. Kimmel
Peter P. Roy-Byrne
Deborah S. Cowley

Selective serotonin reuptake inhibitors (SSRIs) are now considered the first-line pharmacological treatment for panic disorder (PD) based on their low rate of side effects, lack of dietary restrictions, and absence of tolerance. Similarly, SSRIs and venlafaxine are attractive first-line treatments for social anxiety disorder (SAD). The pharmacological treatments of choice for generalized anxiety disorder (GAD) are buspirone and antidepressants, including SSRIs and SNRIs. Benzodiazepines, although effective for all these disorders, lack efficacy for comorbid depression. Moreover, benzodiazepines carry with them the risk of physiological dependence and withdrawal symptoms. Their greatest utility at present seems to be as an initial or adjunctive medication for patients with disabling symptoms requiring rapid relief and for those unable to tolerate other medications. Chronic treatment with benzodiazepines is generally safe and effective but should probably be reserved for patients who are nonresponsive or intolerant to other agents. Larger trials are necessary to determine whether pharmacological agents might be useful as monotherapies, or as adjuncts to exposure psychotherapy sessions, for specific phobia.

INTRODUCTION

Since the early 1980s, when the third edition of the *Diagnostic & Statistical Manual of Mental Disorders* (DSM-III; American Psychiatric Association [APA], 1980) subdivided neuroses into the separated domains of panic, generalized anxiety, and phobias, we have seen a growing appreciation of the important role of pharmacotherapy in the treatment of these syndromes and an accumulating body of evidence documenting the efficacy of specific classes of medication for specific anxiety disorders. This chapter reviews the clinical characteristics and pharmacotherapy of four major anxiety disorders: PD, GAD, SAD, and specific phobia. Selected literature will largely focus on the most rigorously designed studies. Other levels of evidence will be cited only to address key clinical issues not yet studied in randomized controlled trials (RCTs).

PANIC DISORDER

Panic attacks are sudden, unexpected bursts of extreme anxiety accompanied by at least four cardiorespiratory,

gastrointestinal, otoneurological, autonomic, or cognitive symptoms. PD is characterized by the presence of recurrent panic attacks, at least some of which are spontaneous (i.e., unexpected), followed by a month of persistent anxiety about having attacks, concern about the implications of attacks (often marked by hypochondriacal preoccupations), or avoidance of situations that the individual feels will bring on attacks. *DSM-5* (APA, 2013) has removed the *DSM-IV*'s specifications about PD in the presence or absence of agoraphobia. In the *DSM-5* system, agoraphobia is its own separate diagnosis. Because virtually all medication trials have included patients with PD complicated by phobic avoidance, the studies in the following review of antipanic agents are likely applicable to these individuals.

Although one in seven people will experience a panic attack in their lifetime, the diagnosis of PD involves recurrent attacks along with preoccupation or behavioral changes and has prevalences in the general population of 1.5% (1 month; Eaton, Kessler, Wittchen, & Magee, 1994), 2.3% to 2.7% (12 months; Kessler, Chiu, Demler, Merikangas, & Walters, 2005c), and 3.5% to 4.7% (lifetime; Kessler et al., 2005a). Twice as many women as men are affected, with peak age of onset typically in the late teens and early 20s (Eaton et al., 1994). There are a wide range of prospective genes and gene–environment interactions that may contribute to a risk for PD (Battaglia, 2013; Hamilton, 2009). In addition, stressful life events occur at an increased rate around the time of panic onset (P. P. Roy-Byrne, Geraci, & Uhde, 1986). Interoceptive conditioning and an increased tendency to amplify body sensations, as well as an anxious experience via catastrophic and other cognitive distortions (D. H. Barlow, 2002; Bouton, Mineka, & Barlow, 2001), constitute psychological factors that maintain panic. Hence, PD is likely to involve a heritable biological vulnerability and a series of stressful triggers modulated perhaps by a cognitive style that may have both innate and learned origins.

PD has a high rate of comorbidity with major depressive disorder and vice versa. Indeed, the antidepressant imipramine has been the target of antipanic efficacy studies since the early 1960s. Despite subsequent studies showing the efficacy of benzodiazepines and behavioral treatment in the 1980s, as well as the more recent demonstration of SSRI and serotonin–norepinephrine reuptake inhibitor (SNRI) antipanic efficacy, evidence-based treatment for PD has been poorly integrated into clinical practice. The surprisingly high utilization rate of nonspecific psychotherapy and ineffective medication regimens observed in the 1980s (Taylor et al., 1989) has been improved only modestly in both psychiatric (Goisman, Warshaw, & Keller, 1999), and primary care settings (P. Roy-Byrne et al., 2002; M. B. Stein et al., 2011) with rates of adequate medication (30% to 50%) and cognitive-behavioral treatment (CBT; 10% to 30%) still quite low in these settings. Even among providers who say that they are doing "CBT," the ambiguity of this term, the absence of some core CBT components in their practice, and the inclusion of noncompatible techniques raise questions about how frequently evidence-based guidelines are being followed (Hipol & Deacon, 2013).

The mainstays of pharmacological treatment of PD have been, in order of historical and chronological development, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) in the 1960s and 1970s, high-potency benzodiazepines in the 1980s, SSRIs in the 1990s, and SNRIs in the new millennium. Currently, two benzodiazepines (alprazolam and clonazepam), three SSRIs (paroxetine, fluoxetine, and sertraline), and one SNRI (venlafaxine) have U.S. Food and Drug Administration (FDA) approval for PD. However, other SSRI, heterocyclic, and MAOI antidepressants are also effective, highlighting the fact that there is, in general, poor concordance between established efficacy and approved indication for PD, as well as other anxiety disorders. A large meta-analysis found no difference in the effect sizes between benzodiazepines, TCAs, and SSRIs for panic disorder (Mitte, 2005).

Selective Serotonin Reuptake Inhibitors

Extensive evidence supports the efficacy of SSRIs in the treatment of PD, with a number needed to treat (NNT) of 5 to 8 for the acute phase of treatment (Kumar & Malone, 2008). These agents have replaced benzodiazepines as first-line medication for panic in the judgment of numerous experts (Papp et al., 1997; P. P. Roy-Byrne, Craske, & Stein, 2006; Uhlenhuth, Balter, Ban, & Yang, 1998).

Currently, three SSRIs (paroxetine, sertraline, and fluoxetine) are approved by the FDA for treatment of PD. Type 1, double-blind, placebo-controlled studies, using both flexible and fixed doses, support the

short-term (8 to 12 weeks) antipanic efficacy of paroxetine (Ballenger, Wheadon, Steiner, Bushnell, & Gergel, 1998c; Kampman, Keijsers, Hoogduin, & Hendriks, 2002; Lecrubier, Bakker, Dunbar, & Judge, 1997; Oehrberg et al., 1995; M. Pollack et al., 2007; M. H. Pollack et al., 2007; Sheehan, Burnham, Iyengar, & Perera, 2005; Wedekind et al., 2010), sertraline (Kamijima et al., 2005; Londborg et al., 1998; R. B. Pohl, Wolkow, & Clary, 1998; Pollack, Otto, Worthington, Manfro, & Wolkow, 1998), and fluoxetine (Michelson et al., 1998, 2001). Seven double-blind, placebo-controlled studies have shown efficacy for the now infrequently prescribed SSRI fluvoxamine (Asnis et al., 2001; Black, Wesner, Bowers, & Gabel, 1993; de Beurs, van Balkom, Lange, Koele, & van Dyck, 1995; Den Boer & Westenberg, 1988; Hoehn-Saric, McLeod, & Hipsley, 1993; Nair et al., 1996; Sandmann et al., 1998). Two double-blind, placebo-controlled trials have demonstrated antipanic efficacy for citalopram (Leinonen et al., 2000; Wade, Lepola, Koponen, Pedersen, & Pedersen, 1997), and several trials have shown benefit from the S-isomer of citalopram, escitalopram (Bandelow, Stein, Dolberg, Andersen, & Baldwin, 2007; Stahl, Gergel, & Li, 2003). These SSRI studies have shown effects on symptomatic components of PD, including panic frequency, generalized anxiety, disability, and phobic avoidance, although not all studies measured all of these components.

Continued efficacy over the long term has been demonstrated in placebo-controlled discontinuation designs following acute placebo-controlled trials, for paroxetine over 36 weeks following a 12-week trial (Lecrubier & Judge, 1997), for sertraline over 28 weeks following a 1-year-long open-label extension after a 10-week acute trial (Rapaport et al., 2001), for fluoxetine over 24 weeks following a 10-week trial (Michelson et al., 1999), and for citalopram over 52 weeks following an 8-week trial (U. M. Lepola et al., 1998). In most of these trials, patients who had seen initial benefit continued to improve over the longer term.

There is some controversy about whether PD requires higher SSRI dosing compared to the treatment of depression or just more patience in awaiting efficacy from moderate dosing. Studies have shown that doses of 40 mg paroxetine, 100 to 200 mg sertraline, 10 to 20 mg fluoxetine, 100 to 200 mg fluvoxamine, and 20 to 30 mg of citalopram are effective. Early studies suggested higher doses may be beneficial for paroxetine (Ballenger et al., 1998c) and fluoxetine (Michelson et al., 2001) and perhaps counterproductive for sertraline at the 200-mg dose (Londborg et al., 1998). In a more recent study, sertraline (maximum dose 100 mg) or escitalopram (maximum dose 15 mg) was employed in a 6-week, open-label trial. Patients with continued panic symptoms were enrolled in a 6-week RCT wherein half of the patients were allowed dose increases of up to 200 mg sertraline or 30 mg escitalopram and half of the patients were continued on the initial dosing paradigm. Increased dose did not increase efficacy (Simon et al., 2009).

In some of the earliest studies of imipramine for panic, it was noted that the response rate at 6 months was higher than the response rate at 3 months (Zitrin, 1983). Similarly, the time course of effect for SSRIS has been shown to be delayed. In the various studies, superiority to placebo has emerged, depending on the specific outcome being measured, as early as 2 weeks (Pollack et al., 1998) and as late as 4 weeks (Ballenger et al., 1998c), with some patients responding later, at 9 to 12 weeks (Michelson et al., 2001; Oehrberg et al., 1995). Early improvement does seem to predict more complete response—that is, remission—at the end of the acute trial (Pollack et al., 2002).

Early overstimulation was noted with fluoxetine in open reports (Schneier et al., 1990), prompting recommendations for low (5-mg) starting doses, although other trials began at 10 mg with fewer problems (Michelson et al., 2001). Such effects have been infrequently noted with the other SSRIs. For example, only 2 of 80 sertraline patients experienced overstimulation in one study (R. B. Pohl et al., 1998).

The side effect burden with SSRIs has been much less severe, with higher percentages of patients completing treatment (82%), than in studies of TCAs (69%) (Bakker, van Balkom, & Spinhoven, 2002). However, abrupt withdrawal of SSRIs has been associated with a withdrawal syndrome marked by irritability, nausea, dizziness, and headache in the case of both fluvoxamine (Black, Wesner, & Gabel, 1993) and paroxetine (Oehrberg et al., 1995). This is probably due to their relatively shorter half-life compared with fluoxetine and sertraline, although similar but milder symptoms have been observed with sertraline discontinuation (Rapaport et al., 2001). The common practice of switching patients to the longer-acting fluoxetine before discontinuation has not been tested in a controlled trial. Patients taking SSRIs for PD also demonstrate statistically significant

increases in body weight and rates of sexual dysfunction (Dannon et al., 2007).

One interesting meta-analysis showed a greater effect size for serotonergic antidepressants than for both TCAs and benzodiazepines (W. Boyer, 1995), with the effect reduced, but still maintained, when only studies using high-dose imipramine or alprazolam were compared. However, other meta-analyses have failed to show a clear efficacy advantage of antidepressants over benzodiazepines (den Boer, 1998), or for SSRIs over TCAs (Bakker et al., 2002; Mitte, 2005), although three studies using direct comparisons have shown SSRI superiority to noradrenergic heterocyclics (fluvoxamine vs. maprotiline, Den Boer & Westenberg, 1990; zimelidine vs. imipramine, L. Evans, Kenardy, Schneider, & Hoey, 1986; and clomipramine vs. desipramine, Sasson et al., 1999). These findings suggest, but do not conclusively demonstrate, that serotonergic antidepressants may have an advantage as antipanic agents.

Serotonin–Norepinephrine Reuptake Inhibitor

Venlafaxine (mean dose 166 mg) proved effective in uncomplicated PD in two placebo- controlled trials (Bradweijn, Stein, Salinas, Emlien, & Whitaker, 2005; Pollack et al., 1996) and garnered FDA approval for PD. Pollack's follow-up work on venlafaxine extended-release added more weight to the evidence (M. Pollack et al., 2007) Not every trial of venlafaxine has demonstrated a statistically significant reduction in the number of panic-free patients, although beneficial effects on other panic measures were still demonstrated (Bradweijn et al., 2005; Liebowitz, Asnis, Mangano, & Tzanis, 2009). There exist no placebo-controlled trials in PD for duloxetine, desvenlafaxine, or levomilnacipran.

Tricyclic (Heterocyclic) Antidepressants

Extensive evidence supports the efficacy of TCAs, including the predominantly serotonergic TCA clomipramine, in PD. Their effect size is equal to that of SSRIs (Mitte, 2005). The initial demonstration of reduction in panic attacks, but more variable and sometimes less robust effects on anticipatory anxiety and phobic avoidance, with imipramine compared with a placebo has been replicated many times since the 1960s (D. F. Klein, 1964). Designs have varied in duration (6 weeks to 9 months), dosage (i.e., whether minimally effective doses of 150 mg have been used), breadth of symptoms measured (panic, phobia, disability), sample size, proportion of sample with comorbid phobia and depression, and use of additional behavioral therapies. Sixteen placebo-controlled trials have conclusively shown that TCAs are superior to a placebo for reduction of panic attacks and associated anxious and phobic symptomatology, 11 for imipramine (D. H. Barlow, Gorman, Shear, & Woods, 2000; Cross-National Collaborative Panic Study, Second Phase Investigators, 1992; M. Mavissakalian & Michelson, 1986; M. R. Mavissakalian & Perel, 1995; Nair et al., 1996; Schweizer, Rickels, Weiss, & Zavodnick, 1993b; Sheehan, Ballenger, & Jacobsen, 1980; Taylor et al., 1990; Uhlenhuth, Matuzas, Glass, & Easton, 1989; Zitrin, Klein, & Woerner, 1978; Zitrin, Klein, Woerner, & Ross, 1983) and 5 for the nonselective serotonin-reuptake inhibitor clomipramine (Broocks et al., 1998; Caillard, Rouillon, Viel, & Markabi, 1999; Fahy, O'Rourke, Brophy, Schazmann, & Sciascia, 1992; Johnston, Troyer, & Whitsett, 1988; Modigh, Westberg, & Eriksson, 1992). One study actually showed clomipramine superiority to imipramine at 12 weeks (Modigh et al., 1992). For imipramine, use of higher doses was more likely to show beneficial effects, and some studies also showed a clear dose–response relationship, with daily doses of 1.5 mg/kg or greater yielding beneficial effects. More recent data have suggested that therapeutic plasma levels are lower for phobia than for panic, explaining the occasionally observed dissociation between effects on these two different measures and further documenting the need for approximately 1.5 to 2.0 mg/kg of imipramine for phobia and 2.0 to 2.5 mg/kg for panic (M. R. Mavissakalian & Perel, 1995). Studies suggesting that lower doses of clomipramine (e.g., 75 mg) could also be effective did not include comparisons with higher doses as in the above imipramine studies.

Time course of effect can only be estimated from reported mean values, which are the average of numerous, somewhat variable, individual time-course profiles. Nonetheless, most studies do not show drug–placebo response differences until week 4, with maximal responses continuing for many measures to the trial's end (usually week 8). Earlier studies actually showed significant continuing improvement in phobic avoidance between weeks 14 and 26, reinforcing Klein's original hypothesis that panic improves before

phobia (Zitrin et al., 1983). Experts reviewing open trial data maintain that peak effects on panic, phobia, and anxiety measures may be delayed until 10 to 12 weeks in many patients, consistent with effects for SSRIs (Lydiard & Ballenger, 1987; Oehrberg et al., 1995). In general, antipanic effects of TCAs may, in some patients, take as long as, if not longer than, traditionally reported antidepressant effects.

Many studies show that TCAs are less well tolerated than, for example, benzodiazepines, with many patients dropping out of clinical trials both early (30% in the large Cross-National Study; more than 50% in some smaller studies) and late (e.g., 20% during maintenance treatment) in one study (D. H. Barlow et al., 2000). A direct comparison showed that imipramine was more poorly tolerated than the SSRI fluvoxamine (Bakish et al., 1996). Even in PD study completers, the side-effect profile advantage of sertraline over imipramine is evident (M. R. Mavissakalian, 2003). Although these trials do not provide clear indications of the reasons, open studies suggest that the most common reason for early discontinuation is overstimulation/jitteriness, and for later discontinuation it is weight gain (Noyes, Garvey, Cook, & Samuelson, 1989). Low initial doses, slower titration, and use of adjunctive benzodiazepines or beta-blockers may attenuate early overstimulation. Elevated heart rate and blood pressure with imipramine may be a problem in older patients or those with cardiac conditions (Taylor et al., 1990).

Few other heterocyclic agents have been studied. Desipramine was superior to a placebo for anxiety and phobia, but not for panic attack frequency reduction, at a mean dose of 177 mg/day in the only study of this agent performed (Lydiard et al., 1993). Based on SSRI class effects, as well as open trials of these other tricyclic agents, it is likely that other TCAs are also effective. Nortriptyline's lower rate of postural hypotension and anticholinergic effects may improve tolerability in some patients. Of other antidepressants in this class, lesser efficacy is suggested for trazodone (than for imipramine and alprazolam) and maprotiline (than for fluvoxamine) (Charney et al., 1986; Den Boer & Westenberg, 1988). Unfortunately, these two studies were not placebo-controlled.

Benzodiazepines

The availability of high-potency benzodiazepines with the introduction of alprazolam in the mid-1980s reversed a prior tendency to view this class of medications as ineffective for PD. Eight placebo-controlled, double-blind trials have found alprazolam to be superior to placebo in the treatment of panic attacks, with 55% to 75% of patients free of attacks at the end point of the study (Ballenger et al., 1988; Chouinard, Annable, Fontaine, & Solyom, 1982; Cross-National Collaborative Panic Study, Second Phase Investigators, 1992; Lydiard et al., 1992; Munjack et al., 1989; Schweizer, Patterson, Rickels, & Rosenthal, 1993a; Sheehan, Raj, Harnett-Sheehan, Soto, & Knapp, 1993; Uhlenhuth et al., 1989). Completer analyses showed less striking and sometimes nonsignificant differences because of the high placebo dropout rate. Alprazolam showed similar robust effects on phobic avoidance (six of seven studies), disability (five of five studies), anticipatory anxiety (three of three studies), and generalized anxiety (seven of eight studies). Although daily mean doses of 5 to 6 mg were used in these studies, two studies of lower, 2-mg fixed doses (Lydiard et al., 1992; Uhlenhuth et al., 1989) also showed superiority to a placebo, although panic-free rates were lower than with higher doses (25% to 50% vs. 55% to 75%). An extended-release formulation of alprazolam, given once or twice daily, has been shown to be comparably effective to the immediate-release compound (Schweizer et al., 1993a).

The time course of effect with alprazolam is much more rapid than with antidepressants, with superiority to a placebo generally evident in the first week or two of treatment. While some experts suggest a superiority of these agents for phobia and anticipatory anxiety, panic attacks still appear to improve before phobia with benzodiazepines (Lydiard & Ballenger, 1987). While patients with significant primary major depression were excluded in most trials, patients meeting criteria for major depression judged secondary to PD were included in some studies (mean Hamilton Depression Rating Scale around 15) and in general fared as well as those without a major depression diagnosis (Ballenger et al., 1988).

The tolerability of alprazolam was in general superior to that of imipramine, with greater retention in studies looking at head-to-head comparisons (Cross-National Collaborative Panic Study, Second Phase Investigators, 1992; Schweizer et al., 1993a; Uhlenhuth et al., 1989). The most common adverse effects of alprazolam were sedation or drowsiness, reported in 38% to 75% of patients, and memory

impairment, reported in up to 15% of patients. The frequent lack of patient awareness of memory effects suggests that caution should be used when prescribing these agents in older patients or those needing to perform complex cognitive tasks.

Four placebo-controlled trials have also supported the efficacy of clonazepam for PD and demonstrated a similar rapid time course, spectrum of anxiolytic action, and side-effect profile, with 1 mg being the minimal effective dose (Beauclair, Fontaine, Annable, Holobow, & Chouinard, 1994; Moroz & Rosenbaum, 1999; Rosenbaum, Moroz, & Bowden, 1997; Tesar et al., 1991). A randomized, open, naturalistic trial comparing clonazepam to paroxetine found that clonazepam worked faster, but there was no significant difference in efficacy between the medications by week 8. Although no patients withdrew due to adverse events, the paroxetine group had significantly more adverse events (Nardi et al., 2011). In a 34-month follow-up study, this same group followed patients who had had good results and had opted to continue treatment. They demonstrated a very small, but statistically significant, reduction in the number of monthly panic attacks in the group receiving clonazepam (mean dose 1.9 mg/day) compared to the group receiving paroxetine (mean dose 38.4 mg/day) during the extension period. The paroxetine group continued to have more side effects (Nardi et al., 2012).

One study demonstrated antipanic efficacy for diazepam, and head-to-head comparisons with alprazolam in other non–placebo-controlled studies have shown uniform equivalence with lorazepam (Charney & Woods, 1989; Dunner, Ishiki, Avery, Wilson, & Hyde, 1986; Schweizer, Fox, Case, & Rickels, 1988). One double-blind discontinuation study has documented longer-term efficacy of alprazolam over the course of a year (Dager et al., 1992), and numerous other open naturalistic follow-ups, without a placebo comparison, suggest longer-term efficacy for this and other benzodiazepines.

The main public health concern regarding benzodiazepines has focused on their abuse potential, even though panic patients on long-term treatment do not escalate their doses over time (in fact, their doses go down) and abuse of these drugs does not occur in patients without comorbid alcohol or substance abuse (Garvey & Tollefson, 1986; Nagy, Krystal, Woods, & Charney, 1989). There is also no evidence of tolerance to the therapeutic effects of benzodiazepines in the several long-term studies that have been done. However, virtually all studies show that discontinuation of alprazolam in PD patients is associated with withdrawal symptoms, recurrent panic attacks, and failure to complete the taper in 25% to 50% of patients after as little as 6 to 8 weeks of treatment (J. C. Pecknold, Swinson, Kuch, & Lewis, 1988; P. P. Roy-Byrne, Dager, Cowley, Vitaliano, & Dunner, 1989). The use of a fairly rapid taper (several weeks) in all these studies fails to mirror the current clinical practice of a long, gradual taper, shown to reduce the incidence of withdrawal in one series to 7% (J. Pecknold, 1990). A 1999 study with clonazepam used a longer (although still too rapid) 7-week taper and found symptomatic worsening but no deterioration beyond the original baseline symptom level (i.e., "rebound anxiety"), in contrast to the rebound anxiety noted in all alprazolam studies in at least a portion (approximately 20%) of patients (Moroz & Rosenbaum, 1999). Direct comparisons of alprazolam with imipramine indicate greater taper difficulty and symptom recrudescence over the short term (1 month) with alprazolam (A. J. Fyer, Liebowitz, & Gorman, 1989; Rickels, Schweizer, Weiss, & Zavodnick, 1993b). However, studies showing that relapse rates after imipramine discontinuation gradually increase over 6 months suggest that this difference in short-term (1-month) relapse rates may merely reflect the mirror image of the time course in initial response (i.e., alprazolam more rapid, 1 to 2 weeks, and imipramine more slowly, 1 to 3 months) (Cross-National Collaborative Panic Study, Second Phase Investigators, 1992; M. Mavissakalian & Perel, 1992). This suggests that much withdrawal may in fact be symptom reemergence/relapse, although this relapse is perhaps fueled by bona fide withdrawal reactions.

Monoamine Oxidase Inhibitors

In six double-blind, placebo-controlled studies, classic mixed MAOIs (phenelzine, $N = 5$; iproniazid, $N = 1$) have been shown to be superior to placebo for overall syndrome improvement (panic, anxiety, and phobia) (Lipsedge et al., 1973; Mountjoy, Roth, Garside, & Leitch, 1977; Sheehan et al., 1980; C. Solyom, Solyom, LaPierre, Pecknold, & Morton, 1981; L. Solyom et al., 1973; Tyrer, Candy, & Kelly, 1973). Of note, all of these studies predate the *DSM-III*. Patients were not selected to meet diagnostic criteria

for panic, there were no separate measures of panic frequency obtained, and measures of phobic avoidance or anxiety employed were different from those used in later panic studies. Of the studies, three of the six employed adjunctive exposure treatment or supportive psychotherapy, and one employed adjunctive diazepam. All these studies employed relatively low doses (usually 45 mg phenelzine). Although higher doses are now recommended by most experts, there are limited data to support this. The one modern study that corroborates this idea is a blinded, randomized, 36-patient comparison of tranycylpromine 30 mg/day versus 60 mg/day in patients with comorbid PD and SAD, wherein the higher dose yielded reduced panic attack frequency (Nardi et al., 2010).

The lone study comparing phenelzine to imipramine suggested that phenelzine was superior for phobic avoidance, providing the only empirical evidence to support the impression of many clinicians that this class of medications may have special efficacy for treatment-resistant patients (Sheehan et al., 1980). A number of active drug comparisons, but without placebo, have shown that the selective MAO-A inhibitors brofaromine and meclobamide were equivalent to standard serotonin reuptake inhibitors (fluvoxamine, fluoxetine, and clomipramine), although the only placebo-controlled study failed to show efficacy for meclobamide (Kruger & Dahl, 1999; Loerch et al., 1999; van Vliet, den Boer, Westenberg, & Slaap, 1996).

The time course of MAOI effect is more difficult to estimate precisely from these older studies. Delayed effects are suggested by superior effects at 8 weeks compared with 4 weeks. Of the two studies that lasted 12 weeks, one showed greater efficacy at 12 weeks than at 6 weeks (Sheehan et al., 1980). In general, the time course of effect is likely to be comparable to that seen for other antidepressants.

These medications are well tolerated in the short term due to the absence of early overstimulation effects. However, weight gain, insomnia with paradoxical daytime sedation, sexual dysfunction, and the need to follow a special low-monoamine diet limit their acceptability for some patients. A placebo-controlled study showed that the selective and reversible MAOI brofaromine, which does not require a special diet, is effective for panic, with a 70% response rate, confirming both open trials and a blind comparative trial showing equivalence to clomipramine (Bakish, Saxena, Bowen, & D'Souza, 1993; Garcia-Borreguero et al., 1992; van Vliet, Westenberg, & Den Boer, 1993). However, brofaromine is not available in the United States. No studies have been reported of the selective MAOI selegiline for the treatment of PD.

Other Antidepressants

Nefazodone has been shown to be effective in depression accompanied by panic attacks in a subanalysis of one controlled depression trial (Zajecka, 1996). Mirtazapine has been reported to be effective in two studies, although both were open-label and neither used primary outcomes that were as rigorous as some other PD trials (Boshuisen, Slaap, Vester-Blokland, & den Boer, 2001; Carpenter, Leon, Yasmin, & Price, 1999). A head-to-head, flexible-dose, double-blind trial that compared mirtazapine to fluoxetine noted good efficacy and no difference between the two in several measures, although a measurement of patient global evaluation of phobic anxiety significantly favored mirtazapine. Interestingly, mean doses were low (mirtazapine 18.3 mg and fluoxetine 14 mg). Not surprisingly, there was significantly more weight gain in the mirtazapine group and significant more paresthesias in the fluoxetine group (Ribeiro et al., 2001). The lone placebo-controlled trial of bupropion demonstrated no benefit (Sheehan, Davidson, Manschreck, & Van Wyck Fleet, 1983). Vilazodone and vortioxetine have not been the subject of trials for PD.

Other Agents

Although treatment-resistant PD occurs, it is relatively uncommon when adequate doses of the above medication classes have been tried, especially in conjunction with skilled CBT. Moreover, treatment resistance is much less common than persistent PD due to treatment delivery failure (i.e., failure to access, receive, tolerate, or adhere to appropriate treatment). Few additional classes of medication are effective. Anticonvulsants have been frequently reported effective in open trials, but only gabapentin (Pande et al., 2000), in a secondary analysis focusing on high-severity panic, and valproate, in a small crossover study (Lum, fontaine, Elie, & Ontiveros, 1990), have been shown effective in placebo-controlled designs. In contrast, carbamazepine has been shown to be ineffective in a placebo-controlled design (Uhde, Stein, & Post, 1988). There have been no published,

placebo-controlled trials of pregabalin or second generation (atypical) antipsychotic monotherapy for PD. One small placebo-controlled trial showed that the calcium channel blocker verapamil was an effective antipanic agent (E. Klein & Uhde, 1988), although curiously no other open reports have followed up on this preliminary finding. In placebo-controlled studies, clonidine has not been found to be effective (Uhde et al., 1989), nor has propranolol (Munjack et al., 1989) or buspirone (R. Pohl, Balon, Yeragani, & Gershon, 1989; Schweizer & Rickels, 1988; Sheehan, Raj, Sheehan, & Soto, 1990).

Combined augmentation treatment using multiple agents has been infrequently studied. Early addition of a benzodiazepine to an antidepressant, with withdrawal after 4 to 6 weeks, to speed initial response has been shown to be effective for clonazepam added to sertraline (Goddard et al., 2001) and for alprazolam added to imipramine (Woods et al., 1992). Subsequent discontinuation of the benzodiazepine worsened symptoms in the alprazolam study, probably because of the short half-life of the drug and consequent more severe withdrawal. In a more recent, randomized trial that employed clonazepam augmentation versus CBT augmentation for SSRI nonresponders, only 1 of 9 patients in the clonazepam arm went on to achieve remission (Simon et al., 2009). A small, open-label trial of olanzapine augmentation in the setting of SSRI-resistant panic disorder suggested some benefit (Sepede et al., 2006), but there exist no placebo-controlled trials of second generation (atypical) antipsychotic augmentation for PD. Despite an intriguing study demonstrating that the beta-blocker and serotonin 1A receptor antagonist pindolol, when added to fluoxetine in nonresponsive patients, is superior to placebo (Hirschmann et al., 2000), this strategy is not widely used in clinical practice.

Duration of Treatment/Chronic Treatment

As previously noted, all classes of agents described have been shown to retain their effectiveness over 8 to 12 months (Dager et al., 1992; Lecrubier & Judge, 1997; Michelson et al., 1999; Schweizer et al., 1993b). However, questions remain about the optimal duration of treatment following remission of panic attacks. Current consensus recommendations for treatment duration are 1 to 2 years, based on limited controlled data (APA Work Group on Panic Disorder, 1998; Ballenger et al., 1998a). Many naturalistic studies have shown relapse rates between 30% and 90% following medication discontinuation after 6 to 12 months of treatment (P. P. Roy-Byrne & Cowley, 1995). Relapse in these studies appears strongly related to illness characteristics, specifically Axis I (depression and phobic avoidance) and Axis II comorbidity.

Numerous studies have examined relapse in treatment responders using placebo-controlled discontinuation designs. Among the TCAs, relapse rates were 45% and 65% with imipramine and clomipramine discontinuation after 10 weeks of single-blind placebo substitution (Gentil et al., 1993), 38% within 3 months of placebo substitution of imipramine (M. Mavissakalian & Perel, 1992), and 37% within a year of imipramine discontinuation (M. R. Mavissakalian & Perel, 1999). A meta-analysis of four SSRI trials and two SNRI trials, with follow-up duration of 8 to 52 weeks, documented relapse 8% to 50% of the time with placebo, compared to 3% to 22% of the time with antidepressant continuation. These differences in favor of antidepressant maintenance were statistically significant (Donovan, Glue, Kolluri, & Emir, 2010).

A study of performance on cognitive and behavioral tests in patients with anxiety disorders on long-term benzodiazepine therapy, compared to matched anxious patients not on benzodiazepines, found no meaningful differences (Lucki, Rickels, & Geller, 1986).

Combined Treatment

The impact on speed of improvement when combining CBT and antidepressant is debatable, with no effect seen in acute management in one meta-analysis (Furukawa, Watanabe, & Churchill, 2006) but distinct benefit noted in the acute phase in a 2010 study of SSRI plus CBT (van Apeldoorn et al., 2010). There is ongoing work on the use of D-cycloserine (DCS) to enhance the response to CBT, with a 31-patient, double-blind, placebo-controlled trial demonstrating benefit when 50 mg DCS was given 1 hour prior to the last three sessions of a five-session, exposure-based, CBT sequence (Otto et al., 2010), In contrast, a 39-patient placebo-controlled, randomized trial for patients with agoraphobia and PD engaged in

an 11-session CBT course that included exposure (flooding) sessions found no significant benefit from augmentation with 50 mg DCS (Siegmund et al., 2011).

GENERALIZED ANXIETY DISORDER

GAD is characterized by excessive, frequent, difficult-to-control worry in several life areas, accompanied by significant distress or functional impairment, as well as by at least three of the following six symptoms: restlessness or feeling on edge, easy fatigability, concentration difficulties, irritability, muscle tension, and sleep disturbance. Since its original definition in 1980, GAD has been a problematic diagnosis with changing diagnostic criteria, poor interrater reliability (Di Nardo, Moras, Barlow, Rapee, & Brown, 1993), and high rates of psychiatric comorbidity (Brawman-Mintzer et al., 1993; Breslau & Davis, 1985). Up to 90% of patients with GAD have a lifetime history, and up to 60% a current history, of at least one other psychiatric disorder. The most common comorbidities are SAD, specific phobias, depression, dysthymia, PD, and substance abuse or dependence (Brawman-Mintzer et al., 1993; Wittchen, Zhao, Kessler, & Eaton, 1994). However, there does exist a group of patients with primary or isolated, severe, generalized anxiety associated with significant functional impairment (Kessler, Dupont, Berglund, & Wittchen, 1999). Unlike the earlier variability, the diagnostic criteria remained stable between the *DSM-IV* and *DSM-5*.

GAD usually begins in the teens or early adulthood and is twice as common in women as in men. In the National Comorbidity Survey, GAD had a 12-month prevalence of 3.1% and a lifetime prevalence of 5.7% (Kessler et al., 2005a, 2005c). However, episodes only lasting 1 to 5 months are associated with impairment and comorbidity similar to episodes lasting 6 months (Kessler et al., 2005b), and individuals meeting all criteria except for excessive worry, despite a milder presentation, show substantial impairment, comorbidity, and rates of treatment seeking (Ruscio et al., 2005), suggesting that there is a larger percentage of the population with clinically significant generalized anxiety than these prevalence figures would indicate.

GAD shows significant familial aggregation, with a meta-analysis of family and twin studies yielding an overall heritability of 0.32 (Hettema, Neale, & Kendler, 2001). Stressful life events, especially those involving loss and danger, are associated with the onset of GAD (Kendler, Hettema, Butera, Gardner, & Prescott, 2003).

The high rate of comorbidity, changes associated with successive *DSM* iterations, and the wide range of apparent receptor targets have made it challenging to construct meta-analyses to compare different treatment modalities. Historically, generalized anxiety has been treated with barbiturates, methaqualone, or, since the 1960s and 1970s, benzodiazepines. Since the early 1990s, buspirone and antidepressants have been used for GAD. More recently, second generation (atypical) antipsychotic and pregabalin have been the subjects of placebo-controlled trials. In addition, effective CBT approaches specific for GAD have been developed.

Benzodiazepines

Numerous double-blind, controlled trials have examined the efficacy of benzodiazepines in the treatment of generalized anxiety. For example, in 1978, Solomon and Hart reviewed 78 double-blind studies, concluding that benzodiazepines had not been shown to be superior to a placebo in the treatment of "neurotic anxiety" (Solomon & Hart, 1978).

In 1988, Barlow reviewed eight double-blind 2- to 6-week trials performed between 1978 and 1983 and, using the Hamilton Anxiety Rating Scale (HAM-A) as the outcome measure, found 22% to 62% reductions in score in benzodiazepine-treated patients with generalized anxiety versus 18% to 48% decreases in placebo groups (D. H. Barlow, 1988). He concluded that the effects of benzodiazepines were marginal. However, dropout rates were substantially higher in placebo groups in five of six studies supplying this information, perhaps reflecting lack of efficacy. Two studies performed in the early 1980s suggested that patients with *DSM-III* GAD seen in primary care settings responded equally well to diazepam and a placebo after the first week or two of treatment (Catalan, Gath, Edmonds, & Ennis, 1984; Shapiro, Struening, Shapiro, & Milcarek, 1982). However, diazepam was superior to a placebo for those with the most severe anxiety (Shapiro et al., 1982).

With the evolution of diagnostic criteria for GAD that required both persistent, hard-to-control worrying and a 6-month duration, benzodiazepines were found

to be superior to a placebo in acute (4- to 6-week) double-blind treatment of GAD in most (Borison, Albrecht, & Diamond, 1990; W. F. Boyer & Feighner, 1993; Cutler et al., 1993; Enkelmann, 1991; Laakmann et al., 1998; Rickels, Downing, Schweizer, & Hassman, 1993a; Rickels, Schweizer, Csanalosi, Case, & Chung, 1988b; Rickels, Schweizer, DeMartinis, Mandos, & Mercer, 1997), but not all (J. C. Pecknold et al., 1989; Ross & Matas, 1987), studies. All benzodiazepines appear equally effective (Shader & Greenblatt, 1993). About two thirds of patients experience moderate to marked improvement of anxiety symptoms (usually assessed using HAM-A and Clinical Global Impression [CGI] rating scales) with these medications, with therapeutic effects evident rapidly, within the first 1 to 2 weeks. Doses are lower by approximately half than those used in treating PD (usually the equivalent of 10 to 25 mg/day of diazepam). Benzodiazepines appear particularly effective for somatic anxiety symptoms (Rickels et al., 1982). Patients with minor depressive symptoms respond more poorly to most of these agents (Rickels et al., 1993a), with the possible exception of alprazolam, and both high- and low-anxiety volunteers given lorazepam demonstrated increases in negative emotions and decreases in positive emotions (Garcia et al., 2000).

Side effects of benzodiazepines in GAD are similar to those in PD and include sedation, psychomotor impairment, anterograde amnesia (Lucki et al., 1986), and tolerance, although GAD patients may be less vulnerable than panic patients to discontinuation symptoms, due in part to less severe nature of the anxiety that returns when the benzodiazepine dose is reduced (Ehud Klein, Colin, Stolk, & Lenox, 1994). Of note, as with panic, dose escalation is rare in GAD patients without a history of substance abuse. For example, no dosage increases were observed in 119 anxious patients taking benzodiazepines for an average of 8 years (Rickels, Case, Schweizer, Swenson, & Fridman, 1986).

Azapirones

Buspirone, an azapirone anxiolytic and 5HT-1A receptor partial agonist, was approved in the *DSM-III* era for GAD. Buspirone has been shown in several double-blind studies to be comparable to benzodiazepines, including diazepam, lorazepam, clorazepate, oxazepam, and alprazolam, for the acute treatment of GAD, yielding 30% to 50% reductions in HAM-A scores in 2- to 6-week trials (Ansseau, Papart, Gerard, von Frenckell, & Franck, 1990; Cohn, Bowden, Fisher, & Rodos, 1986; Enkelmann, 1991; Feighner, Merideth, & Hendrickson, 1982; Laakmann et al., 1998; Murphy, Owen, & Tyrer, 1989; Petracca et al., 1990; Rickels, Fox, Greenblatt, Sandler, & Schless, 1988a; Rickels et al., 1982; Strand et al., 1990). Other azapirones, including ipsapirone and gepirone, have also proved effective in placebo-controlled, double-blind trials but are not available in the United States (Borison et al., 1990; W. F. Boyer & Feighner, 1993; Cutler et al., 1993; Rickels et al., 1997).

In comparison with benzodiazepines, buspirone has a delayed (2- to 4-week) onset of action, may affect psychic anxiety symptoms to a greater extent than physical symptoms, and has the advantage of being nonsedating and without evidence of tolerance or withdrawal symptoms (Feighner & Cohn, 1989; Rickels et al., 1982). Common side effects of buspirone include nausea, dizziness, and headaches. Average therapeutic doses are 20 to 45 mg/day, although doses of up to 60 mg/day may be necessary. It should also be noted that busprione has a 2- to 3-hour half-life, necessitating TID dosing in some patients. Buspirone displays antidepressant effects in patients with comorbid depression, usually at higher doses of 45 to 60 mg/day (Gammans et al., 1992).

In general, patients on chronic benzodiazepine treatment do not respond well when switched to buspirone (DeMartinis, Rynn, Rickels, & Mandos, 2000; M. Lader & Olajide, 1987). For example, in a reanalysis of treatment results in 735 patients with GAD treated with buspirone, a benzodiazepine, or a placebo, clinical improvement was similar with buspirone versus benzodiazepine treatment in those patients with no prior history of benzodiazepine treatment and in those whose benzodiazepine treatment had ended a month or more prior to the study. In those with recent benzodiazepine treatment (within the past month), there was greater attrition with buspirone treatment due to lack of efficacy and less clinical improvement than with benzodiazepine treatment (DeMartinis et al., 2000). A double-blind study of 44 GAD patients switched to buspirone versus a placebo after 5 weeks of lorazepam treatment, with lorazepam tapered during the first 2 weeks of buspirone-versus-placebo treatment, was more

promising and showed that buspirone was superior to a placebo and comparable to lorazepam in anxiolytic effects (Delle Chiaie et al., 1995). There was no evidence of benzodiazepine withdrawal symptoms. However, the duration of lorazepam treatment was quite short. In a study examining imipramine versus buspirone versus placebo for treatment of 107 patients with GAD who had used benzodiazepines for an average of 8.5 years, the success rate of the 4- to 6-week benzodiazepine taper was significantly higher with imipramine (82.6%) than with buspirone (67.9%) or placebo (37.5%) (Rickels et al., 2000a).

A meta-analysis in the *DSM-IV* era noted buspirone to have an effect size equal to that of venlafaxine for GAD (Mitte, 2005). Similarly, a *DSM-IV*–era Cochrane Database review of azapirones for GAD noted a NNT of 4.4 (Chessick et al., 2006).

Antidepressants

When PD and GAD initially were described as distinct anxiety disorders, PD was postulated to differ from GAD in responding to antidepressant treatment. However, since the mid-1980s, a number of antidepressants, including venlafaxine, duloxetine, imipramine, trazodone, paroxetine, escitalopram, and sertraline, have been shown in double-blind trials to be effective in treating GAD (Allgulander et al., 2008; J. R. Davidson, DuPont, Hedges, & Haskins, 1999; Gelenberg et al., 2000; Haskins, Rudolph, Pallay, & Derivan, 1998; Hoehn-Saric, McLeod, & Zimmerli, 1988; Kahn et al., 1986; Montgomery, Tobias, Zornberg, Kasper, & Pande, 2006; Rickels et al., 1993a; Rickels, Pollack, Sheehan, & Haskins, 2000b; Rocca, Fonzo, Scotta, Zanalda, & Ravizza, 1997). Venlafaxine, duloxetine, paroxetine, and escitalopram are now approved by the FDA for treatment of this disorder.

In an early double-blind trial, Kahn and colleagues (1986) reported the then-surprising result that imipramine performed better than chlordiazepoxide in the treatment of nondepressed outpatients retrospectively diagnosed as having GAD. Following up on this, Hoehn-Saric and colleagues (1988), in a study of nondepressed patients with GAD, found that imipramine was comparable to alprazolam after the first 2 weeks of treatment. Imipramine was more effective in reducing psychic anxiety symptoms such as obsessionality, dysphoria, negative anticipatory thinking, and interpersonal sensitivity; alprazolam was superior in alleviating cardiovascular and autonomic symptoms.

Rickels and colleagues (1993a) compared imipramine (mean dose 143 mg/day), trazodone (mean dose 255 mg/day), diazepam (mean dose 26 mg/day), and a placebo in 230 patients with GAD treated for 8 weeks. Although all active treatments were superior to the placebo, diazepam yielded the most improvement in anxiety ratings for the first 2 weeks and imipramine was the most effective treatment thereafter, with 73% of patients moderately or markedly improved compared with 69% on trazodone, 66% on diazepam, and 47% on the placebo. Once more, antidepressants reduced psychic anxiety symptoms to a greater extent than did diazepam. Patients on antidepressants also reported more side effects.

Rocca and colleagues (1997) compared paroxetine, imipramine, and 2′-chlordesmethyl-diazepam in 81 patients with GAD. All three treatment conditions resulted in significant clinical improvement in about two thirds of patients. As in prior studies, the benzodiazepine resulted in more rapid improvement, but the antidepressants resulted in more improvement by week 4. In addition, paroxetine and imipramine were most effective for psychic anxiety symptoms, whereas 2′-chlordesmethyl-diazepam was superior for somatic symptoms. Imipramine's NNT for GAD has been subsequently calculated as 4 (Kapczinski, Lima, Souza, & Schmitt, 2003).

A number of controlled studies have now demonstrated the efficacy of SSRIs, and the combined serotonin and norepinephrine reuptake inhibitors, duloxetine and venlafaxine, in the treatment of GAD. Promising observations in double-blind trials that venlafaxine was more effective than placebo in treating symptoms of anxiety in depressed outpatients (Feighner, Entsuah, & McPherson, 1998; Khan, Upton, Rudolph, Entsuah, & Leventer, 1998) then led to type 1 double-blind, placebo-controlled trials, which established the efficacy of this agent in nondepressed patients with GAD (J. R. Davidson et al., 1999; Gelenberg et al., 2000; Haskins et al., 1998; Rickels et al., 2000b). Venlafaxine extended-release, in doses of 75 to 225 mg/day, yielded significantly greater decreases in anxiety than placebo within the first 2 to 3 weeks of treatment. Davidson and colleagues found that venlafaxine extended-release (75 or 150 mg/day) was more effective than buspirone (30 mg/day) throughout their 8-week study (J. R. Davidson et al., 1999), and Gelenberg and colleagues (2000) showed

persistent treatment gains over 28 weeks of treatment, with response rates (defined as a 40% decreases in HAM-A score or CGI of 1 or 2) at weeks 6 from 28% to 69% with venlafaxine extended-release 75 to 225 mg/day compared with 42% to 46% in the placebo group. This efficacy was replicated in a more recent, placebo-controlled trial as well (Montgomery et al., 2006). Patients treated in venlafaxine efficacy studies showed decreases in both psychic and somatic anxiety symptoms, although, consistent with prior antidepressant trials, effects on psychic anxiety were more pronounced (Meoni, Hackett, & Lader, 2004). Duloxetine, which also obtained FDA approval for GAD in the *DSM-IV* era, appears to have equal tolerability and efficacy compared to venlafaxine (Allgulander et al., 2008).

Eight- to twelve-week trials have demonstrated efficacy of paroxetine 20 to 50 mg/day (Pollack et al., 2001; Rickels et al., 2003), sertraline 50 to 150 mg/day (Allgulander et al., 2004a; Ball, Kuhn, Wall, Shekhar, & Goddard, 2005), and escitalopram 10 to 20 mg/day (J.R. Davidson, Bose, Korotzer, & Zheng, 2004; Goodman, Bose, & Wang, 2005), with response rates of 50% to 70% compared with 30% to 40% on placebo. Paroxetine significantly reduced the HAM-A anxious mood item compared with placebo as early as week 1, produced greater reductions in disability than placebo, and was equally effective at 20-mg/day and 40-mg/day doses (Pollack et al., 2001; Rickels et al., 2003). Pooled paroxetine data that included 1,800 patients demonstrated a NNT of 10 for GAD, with a mean dose of 24.3 mg/day (Rickels, Rynn, Iyengar, & Duff, 2006).

Escitalopram, in pooled results from three double-blind, placebo-controlled trials, differed significantly from placebo in total HAM-A score and in psychic anxiety by week 1 at a dose of 10 mg/day (Goodman et al., 2005) and was associated with improved quality of life (D. J. Stein, Andersen, & Goodman, 2005). Escitalopram's efficacy at 20 mg/day (Coric et al., 2010) and its positive impact on quality of life in pooled data (Demyttenaere, Andersen, & Reines, 2008) continue to be evident in more recent studies.

Escitalopram failed to demonstrate statistical, intent-to-treat, significance due to a high dropout rate in a recent study of patients over 60 years old (Lenze et al., 2009). Interestingly, citalopram also failed to demonstrate statistical significance for remission in another, small study of patients over the age of 60 with GAD (Lenze et al., 2005).

In one study sertraline treatment significantly decreased both psychic and somatic anxiety scores, although its effect on psychic anxiety was more pronounced (Dahl et al., 2005). Other placebo-controlled trials have demonstrated sertraline's efficacy at an average of 95 mg/day (Allgulander et al., 2004a) and 149 mg/day (Brawman-Mintzer, Knapp, Rynn, Carter, & Rickels, 2006).

A controlled 8-week study directly comparing paroxetine and sertraline demonstrated similar efficacy and tolerability for both agents (Ball et al., 2005), whereas a 24-week comparison of escitalopram and paroxetine demonstrated similar reductions in HAM-A scores but a significantly higher rate of discontinuation due to adverse events with paroxetine (22.6%) versus escitalopram (6.6%) (Bielski, Bose, & Chang, 2005). A meta-analysis of venlafaxine extended-release trials, a paroxetine trial, and a fluoxetine trial demonstrated no difference between venlafaxine and the SSRIs (Mitte, 2005). This result was reaffirmed in a meta-analysis of escitalopram, paroxetine, sertraline, fluvoxamine, and venlafaxine extended-release (Hidalgo, Tupler, & Davidson, 2007).

Other antidepressants show promise as treatments for GAD. For example, an open, 12-week trial of mirtazapine 30 mg/day in 44 outpatients with GAD yielded a response (defined, as in most of the SSRI trials described above, as a 50% or greater decrease in HAM-A score and a CGI improvement score of 1 or 2) in 79.5% of patients (Gambi et al., 2005). Bupropion extended-release demonstrated comparable efficacy to escitalopram in a small, double-blind study (Bystritsky, Kerwin, Feusner, & Vapnik, 2008), but there are no placebo-controlled trials of bupropion.

Although the SSRIs and SNRIs are associated with gastrointestinal side effects, weight gain, and sexual side effects, their favorable tolerability in comparison to TCAs (Brambilla, Cipriani, Hotopf, & Barbui, 2005), their efficacy for comorbid depression, and the lack of risk of tolerance and dependence make them first-line treatments for this condition.

Other Medications

About one third of patients with GAD remain symptomatic despite treatment. Thus, studies have attempted to find pharmacological treatments with novel mechanisms of action and augmentation

strategies to improve our ability to help treatment-resistant patients.

Studies performed prior to 1980 showed no efficacy of beta-blockers for the treatment of generalized anxiety (Hayes & Schulz, 1987). Another double-blind, placebo-controlled trial was more promising (Meibach, Mullane, & Binstok, 1987). This 3-week, multicenter study of propranolol (average maximum dose 189 mg/day) versus chlordiazepoxide (average dose 50 mg/day) versus a placebo in 417 outpatients with "anxiety sufficiently severe to warrant treatment with an anxiolytic agent" showed the superiority of both active drugs but fewer side effects with propranolol than with chlordiazepoxide. Surprisingly, propranolol was particularly effective in reducing psychic symptoms of anxiety. Open trials of betaxolol, a long-acting beta-blocker that enters the central nervous system, in 18 inpatients and 13 outpatients with anxiety disorders (including 16 inpatients and 11 outpatients with GAD) showed marked improvement in anxiety ratings in most patients (Swartz, 1998). Nevertheless, most experts continue to feel that beta-blockers are not an effective primary treatment for GAD and should be reserved for use as an adjunct, particularly in patients with prominent autonomic symptoms.

A multicenter, double-blind, 4-week trial of hydroxyzine (50 mg/day) versus a placebo in 133 GAD patients displayed significantly greater reductions in anxiety in the hydroxyzine group, although side effects were more common than in the placebo group (Ferreri, Hantouche, & Billardon, 1994). Similarly, both hydroxyzine (50 mg/day) and buspirone (20 mg/day) were superior to placebo in a double-blind, multicenter, 4-week trial in a total of 244 GAD patients (M. Lader & Scotto, 1998). A 12-week study comparing hydroxyzine (50 mg/day), bromazepam (6 mg/day), and placebo in 334 patients with GAD demonstrated significantly higher response and remission rates with both active drugs than with placebo (Llorca et al., 2002; Pande et al., 2003).

A meta-analysis of seven placebo-controlled trials of pregabalin suggested small effect sizes of 0.35 for psychic anxiety and 0.24 for somatic anxiety symptoms in GAD (Boschen, 2011). Dosing in placebo-controlled studies of pregabalin has ranged from 150 to 600 mg/day. Several studies have found no efficacy with dosing at the 150-mg end (Feltner et al., 2003; Pande et al., 2003), whereas a review of six double-blind, placebo-controlled trials suggested that the efficacy of pregabalin plateaus at 300 mg/day (Lydiard, Rickels, Herman, & Feltner, 2010).

Some trials have sought to compare pregabalin to benzodiazepines. In one, patients with GAD were treated for 4 weeks with alprazolam 1.5 mg/day, placebo, or one of three doses of pregabalin (300, 450, or 600 mg/day). Both alprazolam and pregabalin were superior to placebo in decreasing psychic and somatic anxiety symptoms, and the 300-mg/day dose of pregabalin was superior to both placebo and alprazolam at treatment end point. At 300 mg/day, the discontinuation rate due to side effects in this study was 3%, with the most common being somnolence, dizziness, and dry mouth (Rickels et al., 2005). Pregabalin's superiority to benzodiazepines has not been universal, however. For example, pregabalin did not significantly beat lorazepam 2 mg TID in the aforementioned studies by Pande and colleagues (2003) and Feltner and colleagues (2003). A placebo-controlled trial employing pregabalin while attempting a gradual benzodiazepine taper in patients with GAD was hampered by a high dropout rate, although some benefits were suggested (Hadley, Mandel, & Schweizer, 2012).

Two trials have compared the efficacy of venlafaxine to pregabalin. The first randomized patients to placebo, venlafaxine 75 mg/day, pregabalin 400 mg/day, or pregabalin 600 mg/day. Only the pregabalin 400-mg/day dose demonstrated efficacy on all primary and secondary measures, with venlafaxine 75 mg/day failing to show efficacy for somatic symptoms of anxiety compared to placebo. The authors note, however, that the low dose and the 6-week duration of the study may have affected venlafaxine's efficacy (Montgomery et al., 2006). The second trial, compared flexibly dosed venlafaxine extended-release (mean maximal daily dose 155 ± 60 mg) to flexibly dosed pregabalin (mean maximal daily dose 424 ± 118 mg) and placebo. Pregabalin, but not venlafaxine extended-release, significantly beat placebo on the HAM-A at the end of the 8-week trial. Venlafaxine-treated patients were significantly more likely to report a severe adverse event (20%) than patients on placebo (7.8%). Only 9.1% of patients on pregabalin reported a severe adverse side effect (Kasper et al., 2009).

Finally, an 8-week, double-blind, placebo-controlled trial of refractory GAD employed pregabalin as an adjunct to open-label treatment with venlafaxine extended-release, escitalopram, or paroxetine. By the end of the 8-week study, with mean daily pregabalin dose reaching 496 mg, HAM-A

responder, but not remission, criteria were statistically significant (Rickels et al., 2012).

Of 18 patients in an 8-week open trial of riluzole, an antiglutaminergic agent, 15 completed the trial, 12 responded, and 8 remitted (Mathew et al., 2005). Two other, similar, small, open-label trials have suggested some efficacy (Abdallah et al., 2013; Mathew et al., 2008).

A review of three double-blind, placebo-controlled studies of the GABA reuptake inhibitor tiagabine noted that the drug failed to separate from placebo on the primary measure (Pollack, Tiller, Xie, & Trivedi, 2008). An 80-patient, randomized, placebo-controlled study of valproate 500 mg TID found benefit in a 6-week study (Aliyev & Aliyev, 2008). Ocinaplon, an anxioselective GABA receptor ligand, produced greater reductions in anxiety than placebo in a 2-week trial (Lippa et al., 2005). A more recent, 60-patient, placebo-controlled trial (Czobor, Skolnick, Beer, & Lippa, 2010) of ocinaplon also demonstrated a significant HAM-A reduction, although this study was also notable for one case of a serious adverse event (icterus following transaminase elevation) that was deemed possibly related to the medication.

Deramciclane, a camphor derivative and 5-HT2A/2C receptor antagonist, was superior to placebo in an 8-week trial, especially in reducing psychic anxiety symptoms, and was well tolerated, with the most common adverse event being headache (Naukkarinen et al., 2005). Opipramol, a tricyclic compound and D2-, 5-HT2-, and H1-antagonist with high affinity for sigma receptors, was superior to placebo and equivalent to alprazolam in a 4-week controlled trial of 307 patients with GAD (Moller, Volz, Reimann, & Stoll, 2001).

Kava kava, an extract of the plant *Piper methysticum*, used in the South Pacific to induce relaxation and sleep, has a recent positive, placebo-controlled trial for generalized anxiety (Sarris et al., 2013). A review of three other placebo-controlled trials, however, found no benefit (Connor, Payne, & Davidson, 2006). Concerns about hepatotoxicity with kava kava have limited the clinical use of this agent. Passionflower (*Passiflora incarnate*) was equal in effectiveness to oxazepam in one 4-week trial (Akhondzadeh et al., 2001).

A review of three, pooled, quetiapine trials, with dosing ranging from 50 to 300 mg/day, yielded a small effect size of 0.30 in one analysis (Maher et al., 2011) Another review that included four, quetiapine monotherapy, placebo-controlled trials calculated significant odds ratios for both response (2.21) and remission (1.83) in favor of quetiapine (Depping, Komossa, Kissling, & Leucht, 2010). Evidence for quetiapine monotherapy has continued to accumulate, with recent, placebo-controlled trials demonstrating efficacy in the acute phase (Endicott, Svedsater, & Locklear, 2012; Khan et al., 2011), for long-term functioning and sleep quality in maintenance studies of quetiapine responders (Sheehan, Svedsater, Locklear, & Eriksson, 2013), and in patients over 66 years old (Mezhebovsky, Magi, She, Datto, & Eriksson, 2013). The most common side effects of quetiapine in these studies include dry mouth, somnolence, sedation, nausea, dizziness, and headache. A placebo-controlled, active-controlled (escitalopram) study found similar efficacy, although the clinically important adverse impact of quetiapine on weight, glucose, triglycerides, total cholesterol, and LDL-cholesterol was also noted (Merideth, Cutler, She, & Eriksson, 2012). In a 52-week trial of quetiapine extended-release for GAD, 17.4% of patients in the quetiapine group moved from less than two metabolic risk factors to more than three metabolic risk factors, compared to just 7.9% of placebo patients making the same transition (Katzman et al., 2011). Despite quetiapine's evidence of benefit, the metabolic side effects of this drug prevented FDA approval for GAD.

Weight gain was noted in a study of olanzapine (mean dose 8.7 mg/day) versus placebo augmentation for nonresponders to fluoxetine 20 mg/day. This study yielded a greater proportion of responders and a trend toward more remitters in a small sample of 26 patients (Pollack et al., 2006). In 40 patients continuing to experience GAD symptoms despite 4 weeks of treatment with a wide variety of anxiolytics and/or antidepressants, augmentation with risperidone 0.5 to 1.5 mg/day versus placebo in a double-blind, 5-week study led to significantly greater reductions in total and psychic anxiety scores (Brawman-Mintzer, Knapp, & Nietert, 2005). Ziprasidone's lone, placebo-controlled, double-blind study in GAD did not demonstrate statistical significance (Lohoff, Etemad, Mandos, Gallop, & Rickels, 2010). Two small open-label trials of aripiprazole augmentation of an antidepressant suggested some benefit (Hoge et al., 2008; Menza, Dobkin, & Marin, 2007).

Duration of Treatment/Chronic Treatment

Although there is extensive literature regarding acute treatment of generalized anxiety, there is less

information available regarding the long-term efficacy or the optimal duration of treatment.

Few studies have examined results of benzodiazepine treatment beyond the first 6 weeks. Cutler and colleagues (1993) found lorazepam more effective than a placebo after 6 weeks, but not after 8 weeks, of treatment, primarily due to continued improvement in the placebo group. Both alprazolam and lorazepam remained superior to a placebo after 16 weeks in another study (Cohn & Wilcox, 1984). In a study of 101 GAD patients treated with CBT, a placebo, or diazepam for 10 weeks, the greatest improvement was seen in patients receiving a combination of CBT and diazepam, and diazepam alone was more effective than placebo alone (Power, Simpson, Swanson, & Wallace, 1990). Rickels and colleagues (1988a) showed the continued efficacy of clorazepate over a 6-month trial, with no tolerance to anxiolytic effects, but there was no placebo comparison.

Thus, benzodiazepines seem to have continued anxiolytic effects for up to 6 months, but the paucity of longer term placebo-controlled studies leaves us without a clear answer to the question of whether benzodiazepines are superior to a placebo after the initial phase of treatment. Buspirone has shown continued efficacy over a treatment period of 3 to 6 months (Feighner, 1987; Murphy et al., 1989; Rickels et al., 1988b). Long-term treatment with antidepressants has been examined in 6-month trials of venlafaxine and paroxetine, a 24- to 76-week trial of escitalopram, and a 6-month comparison of escitalopram and paroxetine (Allgulander, Florea, & Huusom, 2006; Bielski et al., 2005; Gelenberg et al., 2000; Stocchi et al., 2003). All these studies support the ongoing efficacy of antidepressants for GAD with longer-term treatment. Two (Allgulander et al., 2006; Stocchi et al., 2003) specifically address the issue of relapse using placebo-controlled SSRI discontinuation trials. In a 6-month study of 566 patients with GAD who had responded to 8 weeks of paroxetine, those randomized to long-term placebo treatment were significantly more likely to relapse than those maintained on active medication (39.9% vs. 10.9%), and those on paroxetine were twice as likely to achieve remission (Stocchi et al., 2003). A similar study of 375 responders to acute treatment with escitalopram randomized to double-blind continuation treatment with escitalopram versus placebo showed a 56% relapse rate in patients on placebo versus 19% in those on escitalopram; the rate of discontinuation due to adverse events was similar in the two groups (7% with escitalopram vs. 8% with placebo) (Allgulander et al., 2006).

Longer-term antidepressant treatment is significantly favored ($p < 0.00001$) for relapse prevention in a meta-analysis of SSRI and SNRI studies (Donovan et al., 2010). In this review of treatment responders (two SSRI studies and one SNRI study), the relapse rate over 6 months after switch to placebo was as high as 60%, versus 14% with antidepressant continuation. Similar to the antidepressant data, a 52-week, placebo-controlled maintenance trial for quetiapine monotherapy responders found a 10.2% recurrence of anxiety symptoms with quetiapine continuation versus 38.9% with placebo (Katzman et al., 2011).

Two other studies have addressed the issue of optimal duration of treatment by following patients after discontinuation of effective treatment. Rickels, Case, Downing, and Winokur (1983) found that 50% of patients treated with diazepam for 6 weeks relapsed within 3 months following benzodiazepine discontinuation, and 63% relapsed within a year following discontinuation. In another trial performed by the same group (Rickels et al., 1988b), 45 patients with GAD who responded to 6 months of treatment with clorazepate or buspirone were reevaluated 6 and 40 months after the end of the study. At 6 months, 55% of clorazepate-treated patients and 38% of those treated with buspirone reported moderate to marked anxiety. At 40 months, 34 patients were contacted, and 57% of clorazepate-treated versus 25% of buspirone-treated subjects reported moderate to severe anxiety. These data suggest that for many people, GAD is a chronic illness requiring treatment for longer than 6 months. The apparently better outcome with initial buspirone treatment is interesting but may be attributable to the higher dropout rate in the buspirone group during the initial treatment period, with only the most treatment-responsive patients remaining in the study.

Combined Treatment

CBT has been proved to be an effective treatment for GAD. Given the substantial rate of nonresponse in medication trials, combining psychotherapy and pharmacotherapy seems a promising strategy. A 10-week trial of diazepam, CBT, and combined treatment showed the greatest improvement in the diazepam-plus-CBT group, although similar proportions of patients from each group were taking psychotropic

medications at 6-month follow-up (Power et al., 1990). In a study by Lader and Bond, 60 patients with GAD were randomized to buspirone plus anxiety management, buspirone and nondirective therapy, placebo and anxiety management, or placebo and nondirective therapy (M. H. Lader & Bond, 1998). All treatment groups improved, with no significant differences between groups. More recently, a study of patients more than 60 years old found that combined escitalopram and CBT led to improvement on some, but not all, of the anxiety measures compared to escitalopram alone (Wetherell et al., 2013). In a randomized, but not placebo-controlled, study of patients enrolled in a long-term venlafaxine extended-release study, those who were offered and agreed to receive an 11-sesssion course of CBT did not demonstrate improvement over those who were either not offered or who did not accept the offer of CBT (Crits-Christoph et al., 2011). This type of study has also been tried in reverse. CBT completers who had residual, clinically significant symptoms were randomized to be offered or not offered escitalopram. Of those who were both offered and accepted escitalopram, there was a trend toward improvement in GAD (Schneier, Belzer, Kishon, Amsel, & Simpson, 2010).

SPECIFIC PHOBIA

Specific (formerly simple) phobias are fears and avoidance of discrete objects or situations (e.g., heights, animals, insects, water). These fears are almost always provoked by the specific stressor, are out of proportion to the actual danger, and cause significant impairment, anxiety, or avoidance. Specific phobias are common, with 12-month and lifetime prevalences of 8.7% and 12.5%, respectively (Kessler et al., 2005c, 2005c). Similar to other anxiety disorders, studies suggest some level of genetic contribution for specific phobia (Van Houtem et al., 2013).

The treatment of choice for specific phobias is behavior therapy, specifically systematic desensitization. In a meta-analysis of 33 randomized, psychotherapy trials for specific phobia, most of which included an exposure-based treatment, a moderate to large effect size was demonstrated (Wolitzky-Taylor, Horowitz, Powers, & Telch, 2008).

Pharmacotherapy data are extremely limited. A small, double-blind, placebo-controlled 4-week pilot study examining the efficacy of paroxetine up to 20 mg/day versus placebo for specific phobias showed significant superiority of paroxetine in reducing phobia scores on the Fear Questionnaire and Hamilton Anxiety scale (Benjamin, Ben-Zion, Karbofsky, & Dannon, 2000). A placebo-controlled study of escitalopram suggested benefit, but the sample size was too small to demonstrate statistical significance (Alamy, Wei, Varia, Davidson, & Connor, 2008). It is not known whether the inclusion of a variety of specific phobias, from claustrophobia to odontophobia to acrophobia, in these studies affected the outcomes. Thus, specific therapy trials published in the past few years have tended to focus on a single, specific phobia. For example, a placebo-controlled study of quetiapine enrolled only patients with arachnophobia. A single dose of quetiapine was used during a virtual reality spider challenge. There was no statistically significant benefit seen in the primary outcome measure, although some benefit was seen for somatic anxiety symptoms (Diemer et al., 2013).

There is interest in understanding how medications may interact with the associative learning processes underlying desensitization. There is controlled evidence indicating that use of benzodiazepines may reduce therapeutic effects of exposure treatment for specific phobia (Wilhelm & Roth, 1997). On the other hand, attempts have been made to enhance extinction learning in patients with specific phobia during behavior therapy. A randomized, placebo-controlled study employing yohimbine, a noradrenaline agonist, given 1 hour prior to exposure sessions did not demonstrate benefit (Meyerbroeker, Powers, van Stegeren, & Emmelkamp, 2012). Several placebo-controlled studies have sought to determine whether DCS, given after an exposure session, has merit. However, the results for this strategy in specific phobia have been mixed (Guastella, Dadds, Lovibond, Mitchell, & Richardson, 2007; Nave, Tolin, & Stevens, 2012; Ressler et al., 2004). A recent small but intriguing reanalysis of data from another trial with a null result (Tart et al., 2013) noted that DCS may be beneficial when given to acrophobic patients whose fear was low at the end of an exposure session, but less effective, or even detrimental, when given to patients whose fear was still high at the end of the exposure session (Smits et al., 2013b). This finding may affect the design of future DCS studies in anxiety disorders. Adjunctive DCS, delivered before virtual reality exposure sessions for acrophobia, also has some placebo-controlled evidence (Ressler et al., 2004).

SOCIAL ANXIETY DISORDER

SAD disorder (previously social phobia) is defined as a fear of social or performance situations due to fears of scrutiny and negative evaluation by others. Feared social situations are avoided or endured with distress, causing significant functional impairment. Recent formulations have separated out performance anxiety as a subtype while continuing to view SAD as a spectrum that varies by number and severity of fears (Bogels et al., 2010). Reflecting the most common "specific" form, the *DSM-5* drops the "generalized" specifier and includes a "performance only" specifier. There has also been discussion about whether generalized SAD is distinguishable from avoidant personality disorder (Widiger, 1992), although some cases of avoidant personality seem to align more closely with the schizophrenia spectrum (Bogels et al., 2010). Observations such as these led *DSM-5* authors to continue to include a distinct, avoidant personality disorder diagnosis.

Most of the placebo-controlled, antidepressant trials for SAD took place in the *DSM-IV* era. As mentioned previously, the *DSM-IV* contained a specifier for the "generalized" subtype of SAD. However, even in the *DSM-IV* era, not every SAD medication trial listed the participant subtypes. Even when the subtypes were listed, not every trial sought to exclusively enroll one subtype or the other. In trials that noted and enrolled both subtypes, no consistent difference in medication efficacy was noted.

SAD is common, with a 12-month prevalence of 6.8% and a lifetime prevalence of 12.1% (Kessler et al., 2005a, 2005c). It has an early age of onset, with a peak in childhood and the teenage years (Schneier, Johnson, Hornig, Liebowitz, & Weissman, 1992); it is more common in women than in men (Bourdon et al., 1988); and it is associated with significant disability, with 22% of those with uncomplicated SAD receiving public assistance and more than 50% of social phobics reporting at least moderate functional impairment due to social anxiety (Schneier et al., 1994). In up to 70% of cases, SAD is accompanied by, and commonly precedes, other significant comorbid psychiatric disorders, such as depression, other anxiety disorders, and alcohol abuse and dependence (Schneier et al., 1992).

Behavioral inhibition, characterized by autonomic arousal in response to novelty, increased salivary cortisol, and high norepinephrine activity starting in infancy, and shyness and introversion as a toddler, is strongly associated with later SAD, suggesting an underlying inborn vulnerability in many individuals (Rosenbaum et al., 1991). In addition, family and twin studies suggest that SAD is familial and has a modest heritable component (A. J. Fyer, Mannuzza, Chapman, Liebowitz, & Klein, 1993; Kendler, Neale, Kessler, Heath, & Eaves, 1992; Mosing et al., 2009).

Since the mid-1980s, behavioral and cognitive-behavioral techniques have proven effective in the treatment of SAD (Otto, 1999), and a number of double-blind, placebo-controlled studies have examined the efficacy of psychopharmacological treatments (Muller, Koen, Seedat, & Stein, 2005). Liebowitz and colleagues published the first open and then controlled trials of medication treatment for SAD patients (Liebowitz, Fyer, Gorman, Campeas, & Levin, 1986; Liebowitz et al., 1992). These trials used the beta-blocker atenolol, based on prior reports of the utility of beta-blockers in treating performance anxiety; and the MAOI phenelzine, based on the efficacy of this medication in treating mixed agoraphobia and SAD and its success in treating atypical depression, which shares with SAD the prominent symptom of interpersonal sensitivity. Since these early trials, controlled studies have examined the efficacy of both reversible and irreversible MAOIs, benzodiazepines, serotonin reuptake inhibitors, venlafaxine, pregabalin, gabapentin, and beta-blockers. Several meta-analyses have found moderate to large effect sizes for these medication classes in the acute treatment of SAD (Black et al., 2004; Canton, Scott, & Glue, 2012).

Currently, the SSRIs and venlafaxine are considered the first-line pharmacological treatments, based on their established efficacy for both SAD and common comorbid conditions, in addition to their tolerability, safety, and lack of dietary restrictions or risk of tolerance and withdrawal. Despite this, as in GAD, benzodiazepines remain the most commonly prescribed psychotropic medications for SAD in clinical practice, and most patients remain on them in the long term (Benitez et al., 2008; Vasile, Bruce, Goisman, Pagano, & Keller, 2005).

Serotonin Reuptake Inhibitors

Twenty-five double-blind, placebo-controlled trials of SSRIs for SAD were reviewed in 2000 (van der

Linden, Stein, & van Balkom, 2000), with NNTs ranging from 1.6 to 4.2. Two other meta-analyses, both examining 15 placebo-controlled trials, although one also included venlafaxine, affirmed the efficacy of second-generation antidepressants over placebo (Hansen et al., 2008; Hedges, Brown, Shwalb, Godfrey, & Larcher, 2007).

Paroxetine and sertraline are approved by the FDA for the treatment of SAD, while fluvoxamine and escitalopram have been proven effective in double-blind trials. Citalopram was superior to placebo in a small, 4-week controlled study comparing citalopram, a neurokinin-1 receptor antagonist, and placebo (Furmark et al., 2005). The efficacy of fluoxetine has been examined in three double-blind studies (Kobak, Greist, Jefferson, & Katzelnick, 2002). In one of these, fluoxetine failed to separate from placebo over 14 weeks, but the placebo response rate was high (Kobak et al., 2002). In another comparison of cognitive therapy, fluoxetine plus self-exposure, and placebo plus self-exposure for 16 weeks, cognitive therapy was superior to both of the other groups, which did not differ significantly from each other (Clark et al., 2003). In a third, 14-week trial studying fluoxetine, cognitive-behavioral group therapy (CBGT), and combined treatment, all active treatments yielded significantly higher response rates than placebo at end point and did not differ from each other (Davidson et al., 2004) Response rates were 50.9% for fluoxetine and 31.7% for placebo, providing some support for the efficacy of fluoxetine in SAD. Fluoxetine has also been reported to relieve symptoms of social anxiety emerging during clozapine treatment in one small open trial involving patients with schizophrenia (Pallanti, Quercioli, Rossi, & Pazzagli, 1999).

Paroxetine has demonstrated efficacy for SAD at doses of 20 to 50 mg/day, with significant decreases in Liebowitz Social Anxiety Scale scores as early as week 2, significant reductions in social avoidance and social disability, and overall response rates of 55% to 66% versus 24% to 36% for placebo-treated patients after 11 to 12 weeks (Allgulander, 1999; Allgulander et al., 2004b; Baldwin, Bobes, Stein, Scharwachter, & Faure, 1999; Lepola, Bergtholdt, St Lambert, Davy, & Ruggiero, 2004; Liebowitz, Gelenberg, & Munjack, 2005; Liebowitz et al., 2002; D. J. Stein et al., 1999; M. B. Stein et al., 1998). Pooled data from these eight trials, plus an additional, placebo-controlled study that used paroxetine as an active comparator (Lader, Stender, Burger, & Nil, 2004), yielded an odds ratio for response of 3.41 (Canton et al., 2012). Of note, although some patients responded early, an analysis of three paroxetine trials demonstrated that 46 of 166 patients who were nonresponders at week 8 (27.7%) were responders at week 12, arguing for at least 12-week treatment trials in many patients (D. J. Stein, Stein, Pitts, Kumar, & Hunter, 2002a).

Sertraline trials for 10 to 24 weeks have shown superiority to placebo at doses of 50 to 200 mg/day (Blomhoff et al., 2001; Katzelnick et al., 1995; Liebowitz et al., 2003; Van Ameringen et al., 2001). Four 12-week trials of fluvoxamine, at 100 to 300 mg/day of the regular or controlled-release formulation, have demonstrated superiority of drug over placebo (Davidson et al., 2004; M. B. Stein, Fyer, Davidson, Pollack, & Wiita, 1999; van Vliet, den Boer, & Westenberg, 1994; Westenberg, Stein, Yang, Li, & Barbato, 2004). Finally, in two 12-week studies, escitalopram at 5 to 20 mg/day produced significant reductions in social anxiety scores and disability (Kasper, Stein, Loft, & Nil, 2005; Lader et al., 2004). Response rates with these agents were comparable to those seen with paroxetine and, when reported, ranged from 40% to 55% for the SSRI and 7% to 30% for placebo.

These studies clearly establish that paroxetine, fluvoxamine, sertraline, and escitalopram are effective in the treatment of SAD. It seems likely that other SSRIs also are effective, and that the mixed results for fluoxetine reviewed above may be more a product of study design and sample characteristics than a fundamentally different action of the drug on social anxiety.

Venlafaxine

Extended-release venlafaxine (venlafaxine ER) is FDA approved for SAD. Double-blind, placebo-controlled trials of 75 to 225 mg/day have demonstrated the efficacy of this agent for generalized SAD (Allgulander et al., 2004b; Liebowitz et al., 2005; March, Entusah, Rynn, Albano, & Tourian, 2007; Rickels, Mangano, & Khan, 2004). Venlafaxine treatment, versus placebo, was associated with significantly greater decreases in social anxiety and social and work disability, with reductions in social anxiety occurring as early as week 1 or 2 in one study (Liebowitz et al., 2005). Two studies used paroxetine as an active comparator and showed similar efficacy and rates of adverse events with these two medications (Allgulander et al., 2004b;

Liebowitz et al., 2005). The most common adverse events noted in these two studies were nausea, asthenia, somnolence, and insomnia.

Monoamine Oxidase Inhibitors

Liebowitz and colleagues (1986) reported that 7 of 11 patients with *DSM-III* social phobia showed a "marked" response to phenelzine and the other 4 had "moderate" improvement. Since then, four double-blind, randomized trials have supported the efficacy of phenelzine for SAD (Gelernter et al., 1991; Heimberg et al., 1998; Liebowitz et al., 1992; Versiani et al., 1992). Liebowitz and colleagues (1992) treated 74 patients with SAD with phenelzine (mean dose, 75.7 mg/day), atenolol (mean dose, 97.6 mg/day), or a placebo; by week 8, "response" rates (much or very much improved as assessed by an independent rater) were 64% for phenelzine, 30% for atenolol, and 23% for the placebo.

Gelernter and colleagues (1991), in a study of 65 social phobics (most with specific social phobia) given phenelzine, alprazolam, a placebo, or CBGT, found that all groups improved, perhaps because all patients were encouraged to expose themselves to feared situations. Nevertheless, patients taking phenelzine were more likely than those in the other groups to display functional improvement and to fall below the mean score for the general population on the social phobia subscale of the Fear Questionnaire at the end of 12 weeks. Versiani and colleagues (1992) completed a double-blind trial of phenelzine, the reversible MAOI moclobemide, and placebo. After 8 weeks, phenelzine and moclobemide were both significantly more effective than the placebo, and these gains were maintained for a further 8 weeks. Responders were then maintained on active medication or changed to a placebo. Those switched to the placebo demonstrated significant increases in symptomatology that persisted for at least 5 weeks, a finding suggesting a high rate of relapse. Finally, Heimberg and colleagues (1998) compared 12 weeks of phenelzine, pill placebo, CBGT, and an educational supportive group in 133 patients with social anxiety disorder. Both CBGT and phenelzine were superior to the control conditions, although response for phenelzine was more marked than for CBGT response at 6 weeks.

Thus, double-blind trials support the efficacy of phenelzine in the treatment of SAD. Interestingly, isolated case reports suggest that phenelzine may also be effective in the treatment of conditions related to SAD, such as elective mutism (Golwyn & Weinstock, 1990) and social anxiety secondary to physical disfigurement (Oberlander, Schneier, & Liebowitz, 1994). Other irreversible MAOIs have not been studied in double-blind trials. However, an open trial of tranylcypromine yielded 20 "marked responders" among 29 subjects (Versiani, Mundim, Nardi, & Liebowitz, 1988).

Irreversible MAOIs such as phenelzine have significant side effects, most notably hypertensive crisis, insomnia, weight gain, and sexual dysfunction. Reversible MAOIs, such as moclobemide and brofaramine, bind reversibly, are selective for the A isoenzyme of monoamine oxidase, and have fewer side effects, including a much lower rate of hypertensive crisis. The efficacy of reversible MAOIs in social phobia has been demonstrated in five double-blind, placebo-controlled trials of moclobemide (International Multicenter Clinical Trial Group, 1997; Noyes et al., 1997; Prasko et al., 2006; Schneier et al., 1998; Versiani et al., 1992) and three of brofaramine (Fahlen, Nilsson, Borg, Humble, & Pauli, 1995; Lott et al., 1997; van Vliet et al., 1993), and an open trial suggests that moclobemide is similar in efficacy to the SSRI citalopram (Atmaca, Kuloglu, Tezcan, & Unal, 2002). Unfortunately, despite the promise of the reversible MAOIs moclobemide and brofaromine for social anxiety disorder, these medications are unavailable in the United States. Of note, selegiline, which is a reversible MAOI in low doses, has been reported to be effective for SAD (Simpson et al., 1998b).

Beta-Blockers

Despite an early, promising open study of atenolol for social phobia (Gorman, Liebowitz, Fyer, Campeas, & Klein, 1985) and several studies demonstrating the efficacy of single doses of beta-blockers for treating performance anxiety in nonclinical groups such as musicians and public speakers (Jefferson, 1995), beta-blockers have not proved effective in double-blind trials with patients with different subtypes of SAD. For example, in the comparison of phenelzine, atenolol, and placebo by Liebowitz and colleagues (1992) mentioned above, atenolol was not significantly more effective than a placebo.

Behavior therapy, primarily flooding, was superior to both a placebo and atenolol in one study (Turner, Beidel, & Jacob, 1994), and propranolol showed no advantage over a placebo in a study in which subjects also received social skills training (Falloon, Lloyd, & Harpin, 1981). Pindolol 5 mg TID was studied as a possible augmentation of paroxetine for generalized SAD in a 4-week double-blind trial but was no more effective than placebo (M. B. Stein, Sareen, Hami, & Chao, 2001).

Beta-blockers (e.g., propranolol 10 to 40 mg taken as needed 45 to 60 minutes before a performance) have been shown to reduce autonomic symptoms such as tremor, sweating, and tachycardia in individuals with performance anxiety who do not necessarily meet criteria for SAD (reviewed in Muller et al., 2005). Individuals whose performance anxiety is not characterized by these autonomic symptoms are unlikely to be helped by beta-blockers.

Benzodiazepines

In open trials, both alprazolam, at doses of 3 to 8 mg/day, and clonazepam, 1 to 6 mg/day, have been effective in the treatment of SAD (Davidson, Tupler, & Potts, 1994). The only double-blind, placebo-controlled trial of alprazolam was that by Gelernter and colleagues (1991). Although alprazolam (mean dose, 4.2 mg/day) was not superior to a placebo, this study was complicated by the inclusion of self-directed exposure in all treatment groups. Clonazepam, at an average dose of 2.4 mg/day, decreased social anxiety, interpersonal sensitivity, phobic avoidance, and disability in a 10-week double-blind study of 75 patients with SAD (Davidson et al., 1993). Response rates were 78.3% for clonazepam and 20% for a placebo. Clonazepam was similar in efficacy to CBGT in a 12-week trial (Otto et al., 2000). Clonazepam, at 1 to 3 mg/day, has also been compared to placebo as an adjunctive treatment to paroxetine 20 to 40 mg/day in a randomized, double-blind, 10-week trial (Seedat & Stein, 2004). At 10 weeks, the paroxetine-plus-clonazepam group had a 79% response rate, compared with a 43% response rate for the paroxetine-plus-placebo group, although given the small sample size (19 completers), this difference was significant only at a trend level ($p < 0.06$).

In the most recent study, 181 patients who had an inadequate response to 10 weeks of sertraline were randomized to a 3-month trial of augmentation with clonazepam (up to 3 mg/day), a switch to venlafaxine (mean dose 168 mg), or sertraline plus placebo. The additional 3 months of sertraline yielded a response rate of 17%. The switch to venlafaxine yielded a numerically greater response rate (19%) than sertraline plus placebo. Clonazepam augmentation, however, yielded a response rate of 27%, which was significantly better than the sertraline-plus-placebo group (Pollack et al., 2014).

Use of benzodiazepines for SAD is complicated both by their side effects and by the high rate of comorbid alcohol abuse or dependence in this patient population (Schneier et al., 1992), which may put patients at an increased risk for benzodiazepine abuse and dependence.

Other Medications

Surprisingly, there have been no controlled trials of TCAs for patients with SAD. Although isolated case reports suggest that they may be effective (Benca, Matuzas, & Al-Sadir, 1986), and a large sample of 765 patients with agoraphobia or social phobia responded well to open-label clomipramine (Beaumont, 1977), other anecdotal evidence has been cited suggesting that TCAs are inferior to MAOIs (Liebowitz et al., 1986; Versiani et al., 1988), and an open trial of imipramine (Simpson et al., 1998a) indicated both lack of efficacy and a high dropout rate due to side effects.

Two double-blind trials using buspirone showed no significant improvement with doses averaging 32 mg/day in musicians seeking treatment for performance anxiety (Clark & Agras, 1991) and no difference between buspirone 30 mg/day and placebo in 30 patients with SAD (van Vliet, den Boer, Westenberg, & Pian, 1997). However, an open trial suggests that buspirone may be an effective augmentation agent in partial responders to SSRIs (Van Ameringen, Mancini, & Wilson, 1996).

A randomized, double-blind, placebo-controlled 14-week trial using flexible doses of gabapentin (900 to 3,600 mg/day in three divided doses; mean dose, 2,100 mg/day) in 69 patients with SAD yielded response rates (CGI of 1 or 2) of 32% with gabapentin versus 14% with placebo (Pande et al., 1999). Side effects of gabapentin included dizziness, dry mouth, somnolence, nausea, flatulence, and decreased libido. Pregabalin 600 mg/day, but not lower doses,

was superior to placebo in two double-blind trials in patients with SAD, with the most frequent side effects being somnolence and dizziness (Feltner, Liu-Dumaw, Schweizer, & Bielski, 2011; Pande et al., 2004).

In 16 patients treated with levetiracetam versus placebo, there was a moderate effect size (0.50) for Liebowitz Social Anxiety Scale scores after 7 weeks (Zhang, Connor, & Davidson, 2005). However, in a much larger, 217-patient, placebo-controlled trial, levetiracetam failed to separate from placebo for patients with SAD, generalized type (M. B. Stein et al., 2010).

Based on encouraging open-label studies (Dunlop et al., 2007; Evans et al., 2009), a very small, short, non–placebo-controlled, double-blind crossover study found similar response rates to gabapentin and tiagabine (Urbano et al., 2009).

A placebo-controlled trial of atomoxetine in patients with SAD, but without attention-deficit/hyperactivity disorder, demonstrated no benefit (Ravindran, Kim, Letamendi, & Stein, 2009).

A 16-week, open trial of flexibly dosed topiramate (maximum dose, 400 mg/day) in 23 patients with SAD resulted in rates of remission and response of 26% and 48%, respectively (Van Ameringen, Mancini, Pipe, Oakman, & Bennett, 2004).

Successful treatment of SAD with bupropion (Emmanuel, Lydiard, & Ballenger, 1991), valproic acid (Kinrys et al., 2003), clonidine (Goldstein, 1987), and the dopamine agonist pergolide (Villarreal, Johnson, Rubey, Lydiard, & Ballanger, 2000) has been reported.

A placebo-controlled trial of nefazodone failed to demonstrate statistical significance (Van Ameringen et al., 2007). Mirtazapine monotherapy has a positive placebo-controlled trial (Muehlbacher et al., 2005) and a trial where no benefit over placebo was seen (Schutters, Van Megen, Van Veen, Denys, & Westenberg, 2010). The nonresponsive patients, both those on mirtazapine and those on placebo, of the second trial were then augmented with paroxetine, although the combination of active agents showed no benefit over paroxetine plus placebo (Schutters, van Megen, Van Veen, Schruers, & Westenberg, 2011). Reboxetine (Atmaca, Tezcan, & Kuloglu, 2003) may have some utility in the treatment of SAD.

Olanzapine 5 to 20 mg/day was superior to placebo in a small, double-blind, 8-week trial, with the most common side effects being drowsiness and dry mouth (Barnett, Kramer, Casat, Connor, & Davidson, 2002). A placebo-controlled trial of sulpiride demonstrated no benefit (Bell et al., 2013). A placebo-controlled trial of quetiapine in advance of a public-speaking exposure session for patients with SAD demonstrated no benefit (Donahue et al., 2009). Another small trial of daily quetiapine for SAD also failed to separate from placebo for the primary outcome measures, although some facets of this trial would suggest that a larger study is needed to more clearly define quetiapine's impact (Vaishnavi, Alamy, Zhang, Connor, & Davidson, 2007).

Duration of Treatment/Chronic Treatment

SAD is frequently a chronic illness requiring long-term treatment (Reich, Goldenberg, Vasile, Goisman, & Keller, 1994). Several studies have found continued efficacy of serotonin reuptake inhibitors, venlafaxine, clonazepam, phenelzine, and selective MAOIs with treatment for 5 months or more. For example, sertraline was well tolerated and effective in a 20-week controlled trial (Van Ameringen et al., 2001). In the recent study by Pollack and colleagues (2014), 17% of patients who had an inadequate response to sertraline during an initial 10-week trial went on to demonstrate a response when sertraline was continued for another 10 weeks. Escitalopram was well tolerated and produced further improvement versus placebo between 12 and 24 weeks of treatment at 5 to 20 mg/day (Lader et al., 2004); fluvoxamine controlled-release (CR) 100 to 300 mg/day continued to yield gains in symptomatic improvement and reduction of disability between 12 and 24 weeks of treatment (D. J. Stein, Westenberg, Yang, Li, & Barbato, 2003); and venlafaxine XR at a low dose (75 mg/day) or a high dose (150 to 225 mg/day) was effective throughout a 28-week trial, with no significant differences in outcome between the low- and high-dose groups (M. B. Stein, Pollack, Bystritsky, Kelsey, & Mangano, 2005). In 26 patients with SAD treated with clonazepam for an average of 11.3 months (range, 1 to 29 months), clonazepam was well tolerated; 20 patients were able to reduce their dose and 5 discontinued their medication (Davidson, Ford, Smith, & Potts, 1991b). A trial comparing a placebo and brofaromine followed responders for 9 months (Fahlen et al., 1995). Those on brofaromine showed further symptomatic improvement over this period.

A number of longer-term trials have examined the issue of optimal treatment duration by studying relapse rates with discontinuation of medication at various time points. Connor and colleagues (1998) assigned patients who had responded to 6 months of clonazepam treatment to continued treatment or to a gradual taper (0.25 mg every 2 weeks) with double-blind placebo substitution for 5 months; relapse rates were 0% in the continued-treatment group and 21% in the taper group. However, currently this taper would probably be performed more gradually. In the 9-month brofaromine trial, 6 of 10 placebo-treated patients relapsed, versus none of 22 maintained on brofaromine (Fahlen et al., 1995).

Versiani, Amrein, and Montgomery (1997) reported that, of 59 patients who responded to moclobemide and were continued on treatment for 2 years, 88% deteriorated when the medication was then discontinued. Reinstitution of moclobemide restored the therapeutic response. After another 2 years following the same cohort, medication was discontinued, and up to 6 to 24 months later, 63% of patients had no or mild symptoms, suggesting that longer duration of treatment may reduce relapse after discontinuation. Alcohol abuse was the strongest predictor of negative treatment outcome. In a later follow-up study of patients originally treated acutely with phenelzine or CBGT (Heimberg et al., 1998; Liebowitz et al., 1999), responders were maintained on treatment for 6 months and then followed for a 6-month treatment-free phase. Most patients maintained their gains during the maintenance phase, but relapse rates were higher in phenelzine-treated patients than in the CBGT group once treatment was discontinued.

Four studies have examined relapse rates in patients with SAD who responded to acute treatment with an SSRI and then entered a double-blind phase in which they were maintained on active medication or switched to placebo (Montgomery, Nil, Durr-Pal, Loft, & Boulenger, 2005; D. J. Stein, Versiani, Hair, & Kumar, 2002b; M. B. Stein et al., 1996; Walker et al., 2000). Sixteen paroxetine responders after 11 weeks were randomized to an additional 12 weeks of paroxetine versus placebo in the first of these studies (M. B. Stein et al., 1996). One of eight patients on paroxetine relapsed, compared with five of eight on placebo. Fifty sertraline responders after a 20-week trial were switched to double-blind sertraline versus placebo for an additional 24 weeks and had a relapse rate of 4% on continued sertraline versus 36% on placebo (Walker et al., 2000). Of 323 patients responding to acute treatment with paroxetine, significantly fewer patients relapsed when maintained on 24 weeks of active medication than when switched to placebo (14% vs. 39%; D. J. Stein et al., 2002b). Finally, 371 responders to escitalopram showed a 2.8 times greater risk of relapse when treated with placebo versus medication for another 24 weeks (Montgomery et al., 2005).

Patients who responded to a 10-week, fixed-dose (450 mg) trial of pregabalin were enrolled in a 36-week, double-blind, placebo-controlled continuation trial. Although an administrative issue unrelated to efficacy or safety reasons shut down this study prematurely, the data still significantly favored pregabalin continuation (Greist, Liu-Dumaw, Schweizer, & Feltner, 2011).

Overall, these data suggest that many patients with SAD benefit from continued treatment beyond the acute phase of clinical trials. The optimal duration of treatment remains unclear but appears to be longer than 6 months after acute treatment for a substantial number of people. The World Federation of Societies of Biological Psychiatry and the International Consensus Group on Depression and Anxiety recommend that patients with SAD remain on effective treatment at therapeutic dosages for at least 1 year (Ballenger et al., 1998b; Bandelow, Zohar, Hollander, Kasper, & Moller, 2002).

Combined Treatment

CBT yields large effect sizes in the treatment of SAD (Butler, Chapman, Forman, & Beck, 2006). A confounder in evaluating CBT is the variety of techniques, elements, treatment settings, and group-versus-individual format in the various trials. There are randomized trials that favorably compare CBT to psychodynamic therapy (Leichsenring et al., 2013) and interpersonal therapy (Stangier, Schramm, Heidenreich, Berger, & Clark, 2011).

Two major studies have examined combining CBT with SSRIs to boost response rates. Blomhoff and colleagues (2001) randomized 387 patients with generalized SAD in a primary care setting to sertraline, placebo, sertraline plus exposure therapy, or placebo plus exposure therapy for 24 weeks. Exposure therapy was provided by primary care physicians.

Response rates for both sertraline groups were significantly higher than that of the placebo group, and there was a trend for enhanced efficacy in the sertraline-plus-placebo group. Another study by Davidson and colleagues (2004) compared 14 weeks of fluoxetine, CBGT, CBGT plus fluoxetine, CBGT plus placebo, and placebo in 295 patients with generalized SAD. All active treatments were superior to placebo but similar to each other, with no advantage seen with combined treatment (response rate 54.2% for combined treatment vs. 51.7% with CBGT and 50.9% with fluoxetine). Clearly, further studies of combined treatment are needed.

Two studies have examined the combination of a MAOI and CBGT for SAD. Blanco and colleagues (2010) randomized 128 patients to receive phenelzine, CBGT, CBGT plus phenelzine, or pill placebo. Although both phenelzine and combined treatment significantly beat placebo in certain outcome measures, combined treatment was superior to each monotherapy taken individually, as well as the monotherapies taken as a pool.

Knijnik and colleagues (2008) engaged in a 12-week randomized, but not placebo-controlled, trial of clonazepam with or without psychodynamic group therapy. This 57-patient trial demonstrated benefit for the combined treatment in the Clinical Global Impression-Improvement scale but not the Liebowitz Social Anxiety Scale.

As with specific phobia, DCS has been studied as augmentation to exposure sessions in CBT for SAD. Although an earlier, smaller study by the same group had demonstrated statistically significant benefit for DCS augmentation (Hofmann et al., 2006), a 169-patient trial found no benefit over placebo in either response or remission when DCS was delivered 1 hour in advance of 5 exposure sessions that were part of a larger, 12-session, CBT group treatment (Hofmann et al., 2013). On the other hand, a medium effect size was noted in a similar, but smaller, placebo-controlled trial of DCS 50 mg given prior to exposure therapy sessions (Guastella et al., 2008). As they did with a previously mentioned specific phobia study, Smits and colleagues (2013a) reanalyzed data from the above trial by Hoffman and colleagues and noted a benefit of DCS over placebo for patients reporting low fear at the end of an exposure session, but a detriment compared to placebo in patients who reported high fear at the end of an exposure session. As was the case with specific phobias, this is an emerging intervention that merits further study before more confident conclusions can be made.

SUMMARY

Since the early 1980s, a number of pharmacological treatments have been shown to be effective for PD, GAD, and SAD. SSRIs are now considered by most experts to be the first-line pharmacological treatment for PD based on their low rate of side effects, lack of dietary restrictions, and absence of tolerance and withdrawal symptoms. Similarly, SSRIs and venlafaxine are attractive first-line treatments for SAD. It is important to bear in mind, however, that SSRIs and SNRIs do carry significant adverse side-effect burdens of their own, including weight gain, sexual dysfunction, withdrawal syndromes, the syndrome of inappropriate secretion of antidiuretic syndrome (SIADH), and sleep disturbance. This needs to be considered when deciding whether to recommend pharmacotherapy or CBT as the first intervention. The pharmacological treatments of choice for GAD are buspirone and antidepressants, including SSRIs and venlafaxine. Benzodiazepines, although effective for all these disorders, carry with them the risk of physiological dependence and withdrawal symptoms and ineffectiveness for comorbid depression. Their greatest utility at present seems to be as an initial or adjunctive medication for patients with disabling symptoms requiring rapid relief and for those unable to tolerate other medications. Chronic treatment with benzodiazepines is generally safe and effective but should probably be reserved for patients who are nonresponsive to initial SSRI trials or intolerant to other agents. Controlled trials are necessary to determine whether patients with specific phobias respond to pharmacological agents, particularly serotonin reuptake inhibitors and DCS, as an adjunct to exposure treatments.

Overall, little is known regarding the optimal duration of treatment or long-term outcome of the conditions discussed in this chapter. However, all four disorders begin early in life, often in childhood or adolescence, and follow a chronic or waxing-and-waning course in many people. Thus, further study of treatment of anxiety disorders in children and of long-term management of PD, GAD, specific phobia, and SAD is very important. The major challenges in acute treatment of all of these disorders are to determine the most effective and also cost-effective initial combination

of pharmacological and nonpharmacological treatments and to develop new anxiolytic agents with a rapid onset of action but without the risks of tolerance and withdrawal. For existing agents, particular subtypes of these disorders or types of comorbidity may respond better to some agents than to others, and studies of combination treatments may enhance efficacy, especially in patients who are unresponsive to or only minimally improved with single agents.

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16

Combination Pharmacotherapy and Psychotherapy for the Treatment of Major Depressive and Anxiety Disorders

Cindy J. Aaronson
Gary Katzman
Rachel L. Moster

Clinical wisdom and intuition suggest that when treating major depression and/or anxiety disorders, combining two documented efficacious treatments such as antidepressants and psychotherapy would improve outcome. However, the data do not completely support this conclusion. In this chapter we review randomized clinical trials (RCTs) comparing combined pharmacotherapy and psychotherapy with monotherapy for the treatment of major depressive disorder (MDD), panic disorder (PD), obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and social anxiety disorder (SAD) in adults. Although the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (fifth ed.; *DSM-V*) no longer categorizes PTSD and OCD as anxiety disorders, we have elected to continue to include them in this chapter.

MAJOR DEPRESSIVE DISORDER

The research literature on MDD is divided into three types of studies: acute treatment of nonspecific MDD, acute treatment of specific groups such as the chronically depressed or the elderly, and relapse prevention or maintenance therapy. There have been four review articles of RCTs of combined treatment for MDD since 1997 (Arnow & Constantino, 2003; Hegerl, Plattner, & Möller, 2004; Pampallona, Bollini, Tibaldi, Kupelnick, & Munizza, 2004; Segal, Vincent, & Levitt, 2002) and two meta-analyses (Thase et al., 1997, 2012), which conclude that combined treatment is superior to monotherapy for severely and chronically depressed patients, but not for those with milder forms.

Acute Treatment for Unspecified Depression

Tricyclic Antidepressants

An acute treatment study for nonspecific MDD was conducted by Hollan and colleagues (1992) on 107 outpatients. They compared imipramine with cognitive-behavioral therapy (CBT) and their combination for 12 weeks. All groups showed significant symptom reduction on the Hamilton Rating Scale for Depression (HRSD), but there were no differences in response between combination and each single treatment. It is difficult to interpret these results because only 64 of the 107 subjects completed the treatment, and no intent-to-treat analysis was performed. The overall attrition rate was 40%, without any mention

of breakdown by group. Perhaps the high attrition rate was due to the side effects of imipramine.

In a European trial comparing amitriptyline with clinical management, CBT alone, and the combination of CBT and amitriptyline for 8 weeks, Hautzinger, de Jong-Meyer, and Treiber (1996) studied 191 inpatients and outpatients. Their results were based on an intent-to-treat analysis with a 30% dropout rate; dropout was seen more frequently in the amitriptyline-only group. Dropouts occurred least frequently in the CBT-alone group, significantly later in the study (during the follow-up period) than in the combination group. Hautzinger's group only found a trend toward combination treatment demonstrating a higher response than either single modality alone. Possibly this trend may be accounted for by the inclusion of inpatients, who typically are more severely depressed than outpatients.

Selective Serotonin Reuptake Inhibitors

An Amsterdam study (Dekker et al., 2005) randomized 103 depressed outpatients to one of two conditions: medication and 8 or 16 weeks of psychodynamic supportive psychotherapy. The medication treatment included fluoxetine (20 mg/day) that could then be changed to nortriptyline (50 mg/day up to 150 mg/day) if fluoxetine was not tolerated or was ineffective. A further medication switch was allowed to mirtazapine (15 mg/day up to 45 mg/day) if nortriptyline was either intolerable or ineffective. All medications were maintained for 6 months. The short-term psychotherapy was based on treatment guidelines. Adherence was measured by review of audiotape sessions.

Measures used to determine outcome were the HRSD, the Clinical Global Impression (CGI), the Symptom Checklist (SCL-90), and the Quality of Life Depression Scale. All subjects were moderately depressed with a history of previous depressive episodes, and no current episode lasting longer than 2 years. Although the results showed that both treatments were effective in reducing symptoms over 6 months, the 8-session group achieved remission faster than the 16-session group. There are several limitations to this study, but the most important one is the lack of a control group. Both groups received medication and the same type of psychotherapy, only varying in the duration of treatment. It is difficult to determine how much improvement would be accounted for by the medication and how much by the psychotherapy, since medications were changed for efficacy or intolerance. This study was included in this review because the flexibility of medication treatment more closely resembles clinical practice than usual RCTs and may provide some usefulness to clinicians.

Acute Treatment for Chronic Depression

One of the premier trials included in all the above reviews was conducted by Keller and colleagues (2000), who compared nefazodone, a hybrid serotonin antagonist/reuptake inhibitor, alone; a form of CBT called cognitive-behavioral analysis system of psychotherapy (CBASP); and their combination. For the 12-week trial the researchers recruited 681 outpatients with either MDD for 2 years or longer, current MDD superimposed on dysthymia, or partially remitted recurrent MDD in a current episode. From that initial sample, 519 completed the multicenter study. History of seizures or abnormal EEG findings, severe head trauma, or stroke, suicidality, psychosis, bipolarity, eating disorders, substance use disorders, or severe personality disorders were exclusion criteria. History of nonresponse to nefazodone, CBASP, electroconvulsive therapy, or adequate trials of two different classes of antidepressants were also criteria for exclusion.

CBASP, developed for chronic MDD, is based on aspects of cognitive, behavioral, and interpersonal treatment techniques but is more directive and structured than interpersonal psychotherapy (IPT). The treatment emphasizes social problem-solving methods for dealing with interpersonal problems, and the cognitive work focuses more attention on thoughts about interpersonal interactions, including those with the therapist. The goal of CBASP is to understand how maladaptive patterns of interactions with others foster interpersonal problems. Sessions occurred twice a week during the first 4 weeks, then weekly for 8 weeks. If deemed necessary, the twice-weekly meeting schedule could be continued until week 8.

All patients receiving medication were seen for 15 to 20 minutes weekly, and clinical management was manualized. Pharmacotherapists inquired about symptoms, side effects, and other medication use but did not make any psychotherapeutic interventions. The initial dose of nefazodone was 200 mg/day for

week 1, increased to 300 mg/day at week 2 with subsequent incremental increases of 100 mg/day to a maximum dose of 600 mg/day. A dose of at least 300 mg/day by week 3 was required to stay in the trial.

After randomization of the 681 patients, 226 were assigned to the nefazodone-only group, 228 to the CBASP-only group, and 227 to the combined group. The groups did not differ on demographic and baseline measures. Outcome was measured by the 24-item HRSD; response was defined as a 50% reduction in HRSD score from baseline at weeks 10 and 12, and remission was defined as a score of 8 or less at both weeks 10 and 12.

After 12 weeks, results showed significant reduction in HRSD scores both in the completers and in the intent-to-treat analysis. Using both completer and intent-to-treat analysis, the combined treatment group had a significantly higher response rate than either of the monotherapy groups. The intent-to-treat response rates were 73% for the combined group, 48% for the CBASP group, and 48% for the nefazodone group. The completer response rates were 85% for the combined group, 52% for the CBASP group, and 55% for the nefazodone group. The dropout rate was 24%, with no significant differences among groups. In summary, for chronic depression, combined nefazodone and CBASP was significantly better for achieving response than either therapy alone.

Several additional analyses have been reported using data from this study. Thase and colleagues (2002) looked specifically at symptoms of insomnia and found that nefazodone, in combination and alone, was superior to CBASP at all time points, but the combined treatment was superior to nefazodone alone at the end of 12 weeks of treatment. Psychosocial functioning independent of depressive symptoms was assessed by Hirschfeld and colleagues (2002). Before treatment, the patients demonstrated very low or impaired psychosocial functioning in comparison to community norms. After treatment there was substantial improvement, yet some impairment remained independent of depressive symptoms. Combined treatment had a greater impact on psychosocial improvement than either treatment alone.

Lastly, sexual functioning and satisfaction were considered before and after treatment (Zajecka et al., 2002). At baseline, 65% of the men and 48% of the women had experienced some sexual dysfunction. After treatment, all patients experienced significant improvement in sexual interest and satisfaction, but the combined treatment group demonstrated significantly greater improvement in sexual interest and satisfaction than the CBASP-only group, but not compared to the nefazodone-only group.

The REVAMP trial (Kocsis et al., 2009) was an eight-site study to test the effectiveness of adjunctive CBASP or brief supportive psychotherapy to antidepressant medication compared to continued optimized pharmacotherapy alone for 12 weeks. This two phase trial uniquely treated 808 patients aged 18 to 75 with open-label, stepped pharmacotherapy. The usual exclusionary criteria were followed: bipolar disorders, psychotic disorders, dementia, eating disorders, primary PTSD or OCD, severe personality disorders, and substance dependence. They did allow substance abuse on the condition that participants attend either self-help groups or treatment.

During phase 1 (12 weeks), treatment followed an empirically derived algorithm: sertraline first (if the patient had never failed two adequate trials of selective serotonin reuptake inhibitor [SSRI] and never failed on sertraline); escitalopram (if the patient had failed on sertraline in the past and never failed two adequate trials of SSRI); bupropion (if two failures on SSRI and never failed on bupropion); venlafaxine extended-release (if two failures on SSRI and bupropion); and lastly mirtazapine if all the above had failed. Midway in phase 1, intolerance to any of the treatments moved the patient to the next option in the sequence. If mirtazapine was not tolerated, patients exited the study.

Phase 2 involved augmenting treatment. For partial responders to any of the phase 1 treatments, augmentation was with bupropion or venlafaxine if bupropion was used. For nonresponders to phase 1 treatments, the next step intervention was instituted (from sertraline to escitalopram, escitalopram to bupropion, bupropion to venlafaxine, venlafaxine to mirtazapine). For partial responders and nonresponders on mirtazapine, lithium was added. The second step of phase 2 involved randomizing patients to augmentation of CBASP, brief supportive psychotherapy, or medication only.

Remission in this trial was defined as at least a 60% decrease in HRSD score plus less than 8 on the 24-item version and no longer meeting criteria for MDD for 2 consecutive weeks. Any participants at week 12 who did not meet remission criteria were then eligible to enter phase 2. The medication-only group was seen every other week and visits were based

on the manual used in the Treatment of Depression Collaborative Research study.

Brief supportive psychotherapy (manualized) included reflective listening, empathy, evoking affect, therapeutic optimism, and acknowledgment of patients' assets, but no other interventions using interpersonal, cognitive-behavioral, or psychodynamic approaches were allowed. Both psychotherapy groups received 16 to 20 sessions over 12 weeks.

Of the 808 who entered phase 1, 491 completed 12 weeks and were either partial responders or nonresponders and were randomly assigned to one of three groups (n = 96 medication only; n = 200 CBASP; n = 195 brief supportive therapy). Remission at phase 2 was defined as a 50% decrease in HRSD, a score of less than 8, and Clinical Global Impressions Improvement (CGI-I) of 1 or 2 for two consecutive visits. Partial response was defined as an HRSD score of 8 to 16 but a 50% decrease from baseline and CGI-I of 1 or 2 for two weeks but not consecutively.

The results did not support the hypothesis that CBASP would significantly improve outcome compared to brief supportive psychotherapy or medication alone. Although there was significant improvement in all participants, there was no difference among groups. The authors suggest that the reason for this lack of differentiation, which had been supported in the earlier study (Keller et al, 2000), was due to the optimal use of pharmacotherapy in this trial, mirroring clinical practice. In addition, the participants in this trial were guaranteed medication, not psychotherapy, so perhaps the design selected for those with a preference for medication rather than psychotherapy. The authors also speculate that patients may have had less motivation for entering psychotherapy due to all the medication changes during the stepped treatment.

The researchers tested social problem-solving ability (a major focus of CBASP) to determine whether this differentiated treatment modality. Although the CBASP group experienced significantly greater improvement in social problem solving, this did not predict greater improvement in depressive symptomatology over time.

Chaput and colleagues (2008) randomized 22 of a potential 31 depressed participants who had been treated with an antidepressant plus lithium augmentation for 3 weeks and were considered nonresponders [Hamilton Rating Scale for Depression (HAM-D) score > 18] to either CBT plus quetiapine or CBT plus placebo. This Canadian study was conducted at two sites, with a balanced gender sample (73% female in each group) a mean age of 43.7 and a mean onset of illness of 22.7. Both groups had similar baseline HAM-D, Montgomery Asburg Depression Rating Scale (MADRS), and CGI scores.

Thirty-one patients were enrolled in the first phase of the study; one withdrew before lithium augmentation and another after augmentation. Of the 29 remaining, 5 responded to the lithium and were not continued to the CBT phase, while 2 dropped out, leaving the 22 who were randomized to CBT plus quetiapine or placebo.

CBT treatment was conducted weekly for 12 weeks, with each session lasting 60 minutes, and was based on Beck's model incorporating cognitive restructuring, behavioral techniques, social skills training, and applied relaxation training. Quetiapine was administered with a starting dose of 12.5 mg twice daily. Within the first 14 days, titration to a maximum dose of 200 mg twice a day was instituted in flexible dosing for a stable dose until study completion.

Response was defined as at least a 40% drop in HAM-D or a score less than 18. In this sample, the quetiapine-plus-CBT group significantly improved compared to the placebo-plus-CBT group based on HAM-D. The placebo group experienced more dropouts (only 5 completed 12 sessions) than the quetiapine group (10 completed the 12 sessions), which explains the poor results for the placebo group in the intent-to-treat analysis. When the completer analysis was performed, the CBT-plus-placebo group demonstrated a significant improvement from baseline. The CGI ratings for both improvement and severity demonstrated no significant difference between groups.

In this small sample of 11 patients per group, the combination treatment was more effective than CBT plus placebo based on HAM-D ratings in the intent-to-treat analysis but not compared to those who completed the full course of CBT. The authors explained that their low response rate and the low lithium response rate experienced earlier in the study (only 17%) may have been due to suboptimal treatment duration—only 12 weeks of CBT—while others have used 16 weeks of CBT and at least 3 weeks of lithium treatment. The limited evidence of superiority for combined treatment in this study supports the conclusion that in severely depressed individuals, combined treatment is more effective than monotherapy.

One meta-analysis of studies that included combination treatment for MDD (Thase et al., 1997) lasting 16 weeks compared CBT alone, IPT alone, and both combined with antidepressant medication (imipramine or nortriptyline). The analysis included 595 subjects from six protocols with unipolar depression and was based on a semistructured assessment using *DSM-III* or *DSM-III-R* criteria. All six studies were conducted at the authors' research center between 1982 and 1992. One was a maintenance study of recurrent MDD, a second was a maintenance study for late-life MDD, and the others focused on a specific area such as psychobiology or social factors. Three of the studies included chronically depressed patients whose episode duration lasted 2 or more years. The researchers concluded that combined therapy was superior to psychotherapy alone for recurrent, severe MDD (43% recovery for combined treatment vs. 25% for psychotherapy alone), but there was no difference in less severe depression (48% recovery for combination treatment vs. 37% for psychotherapy alone). In recurrently depressed patients, a shorter duration of illness (time to remission) resulted from combination treatment.

We are including a clinical trial testing cognitive therapy or IPT with and without medication (Peeters et al., 2012) even though it does not qualify as a RCT (no control group) because this points to the issue of treatment choice as a factor in treatment response. This Dutch study allowed MDD patients to choose which treatment they preferred in collaboration with the clinician. The 174 participants (aged 18 to 65) sought treatment from a mood disorders clinic and were diagnosed with a structured interview (SCID) and symptoms were rated using the Beck Depression Inventory (BDI). Inclusion criteria were primary MDD without bipolarity and low suicidality. Primary substance use disorders and psychotic disorder were excluded, but other comorbidity was acceptable.

Treatment sessions (cognitive therapy and IPT) lasted 50 minutes and were conducted weekly for up to 26 weeks. Those participants who also received pharmacotherapy were seen for about 15 minutes to adjust dose and monitor side effects, with no other interventions offered. Typically SSRIs were first-line treatment, followed by switching to another SSRI if needed or to venlafaxine, or a tricyclic with augmentation of lithium in nonresponders.

The 174 participants predominantly chose therapy without medication (cognitive therapy, $n = 63$; IPT, $n = 56$; cognitive therapy plus pharmacotherapy, $n = 34$; IPT plus pharmacotherapy, $n = 21$). The sample was 59% female, mean age 42.4 (SD = 11.1); 36% had chronic depression (lasting more than 2 years) and 53% had another Axis I disorder. At 26-week follow-up 76% of the sample was still available for assessment; there was no significant difference in attrition among groups. At 8 weeks, only 20% remitted, but by 26 weeks 35% remitted. In this study, there was no significant difference in effectiveness between the psychotherapies nor between monotherapy and combined therapy. Effect sizes on the BDI were quite robust (1.3 cognitive therapy; 1.0 cognitive therapy plus pharmacotherapy; 1.5 IPT; 1.0 IPT plus pharmacotherapy). The cognitive therapy group demonstrated a more rapid drop in BDI score than the cognitive-therapy-plus-pharmacotherapy group, but by the end of treatment this difference disappeared. The IPT and IPT-plus-pharmacotherapy groups evidenced parallel drops in the BDI score.

This study applies more realistically to clinical practice settings where patients can choose whether they want medication alone, psychotherapy alone, or the combination. Since less severe pathology was excluded, it is also more realistic to what patients experience in the real world of practice. Treatment duration of up to 26 weeks appears to increase response and remission in patients with chronic and severe MDD with and without comorbidity. Again, although combined treatment is not significantly more effective than monotherapy, it is an effective treatment, as demonstrated by the effect size of 1.0.

Acute Treatment of Major Depressive Disorder in Primary Care

One RCT of MDD in primary care (Mynors-Wallis, Gath, Day, & Baker, 2000) was conducted in England, where 151 subjects were randomized into four treatment groups. The patients in the first group ($n = 39$) were treated by research medical practitioners using a problem-solving technique, those in the second group ($n = 41$) were treated by research nurses using a problem-solving technique, those in the third group ($n = 36$) were treated by research medical practitioners with an SSRI, and those in the fourth group ($n = 25$) were treated by research medical practitioners with medication and by the research nurse, with a problem-solving technique.

The problem-solving treatment was based on the premise that depressive symptoms may be associated with psychosocial problems and that resolving those problems will improve the depressive symptoms. There are six stages to this technique: (a) clarification and problem definition, (b) choice of achievable goals, (c) generation of solutions, (d) choice of solution preference, (e) implementation of chosen solutions, and (f) evaluation. The SSRIs chosen were first fluvoxamine and then paroxetine; dosage was flexible. The medication treatment followed manualized guidelines and did not include any psychological interventions. The monotherapy groups met six times over 12 weeks, weekly for the first 3 weeks (sessions 1 through 3), then intermittently (weeks 5, 7, and 11) for the next 9 weeks. The combined therapy group met with each therapist on the same day. Any patient could receive an extra session if necessary. All treatment occurred in the local health center or in the patient's home.

Outcome was measured by HRSD and the BDI, with clinical interviews and assessments conducted before treatment and at 6 weeks, 12 weeks, and 1 year by blinded raters. In this study, there was no significant difference among treatment groups in outcome at any time point. Only 77% of patients completed treatment, but the investigators managed to collect 12-week data on patients who did not complete treatment. The problem-solving-only group experienced the most dropouts ($n = 14$), while the medication-only and combined treatment groups experienced the fewest dropouts ($n = 6$). At 12 weeks, the response rates ranged between 51% and 67%, perhaps a slightly lower overall response rate than found in other studies using CBT or IPT in combination with medication.

A recent British multicenter study of treatment-resistant depression in primary care, the CoBalT study, tested the addition of CBT to pharmacotherapy (Wiles et al., 2013). Adults, aged 18 to 75, recruited through medical records or direct referral from physicians with MDD, were eligible if they had taken an adequate dosage of antidepressants for 6 weeks and had a BDI score of 14 or more. Bipolar disorder, psychotic disorders, and current substance abuse problems were excluded as well as current or recent CBT treatment. Patients ($n = 469$) were randomized to either CBT or usual care with the expectation that medication use would continue for both groups.

The CBT group received 12 sessions with the option of up to an additional 6 sessions at the discretion of the therapist. Patients in the usual care group might be referred for psychotherapy (counseling or CBT) when the primary care physician deemed it appropriate. CBT followed the manual developed by Aaron Beck for the treatment of depression.

The primary outcome measure was the BDI at 6 months (assessments were also completed at 9 and 12 months). Response criteria were a 50% decrease in BDI score from baseline, while a score of less than 10 was considered remission. The 3-month follow-up assessment included 222 patients in the CBT group and 219 in the usual care group. At 6-month follow-up, 206 in the CBT and 213 in the usual care group completed the BDI.

The mean BDI at baseline was 31.8 and 88% of patients had a previous episode of MDD. There were 94 dropouts from CBT (20 did not attend any sessions, 74 withdrew or were discontinued). By 6 months, median number of sessions attended was 11, with 144 (62%) receiving at least 9 sessions. The results were significant: 46% ($n = 95$) of the CBT group were responders at 6 months compared to 22% ($n = 46$) of the usual care group. The odds ratio for response in the CBT group compared to the usual care group was 3.26. There was also a significant difference in remission between the two groups: 28% of the CBT group compared to 15% of the usual treatment group achieved remission. There was also a significant difference in anxiety as measured by the GAD-7: the patients in the CBT group demonstrated less anxiety as well as less panic. Almost all of the sample was taking medication (93%) at the 6-month follow-up.

At 12 months, significant improvement in the CBT group continued, with 55% ($n = 109$) achieving response and 40% ($n = 78$) achieving remission. In comparison, 31% ($n = 62$) of the usual care group achieved response and 18% ($n = 36$) remitted.

This study demonstrates the effectiveness of adding CBT to pharmacotherapy in patients who do not respond to pharmacotherapy alone after adequate treatment.

Acute Treatment with Adolescents

Prior to the Treatment for Adolescents with Depression Study (TADS, 2004), there were few data testing the efficacy of combined CBT and medication for depressed adolescents. This large RCT conducted at 13 academic and community centers

treated 439 adolescents aged 12 to 17 who met criteria for *DSM-IV* MDD and did not meet criteria for bipolar, conduct, substance, thought, or pervasive developmental disorders. Current use of any antidepressant, failure to respond to two SSRIs, poor past response to CBT for MDD, and intolerance of fluoxetine were exclusion criteria for study participation. In addition, medical conditions that would interfere with safe administration of fluoxetine, high risk for suicide, and inability to speak English were exclusion criteria. Current treatment with psychostimulants for attention-deficit/hyperactivity disorder (ADHD) was allowed if the dosages remained stable throughout the study.

Participants who screened positive and gave consent (n = 439) were randomized to one of four treatment groups: fluoxetine alone (n = 109), CBT alone (n = 111), combined CBT and fluoxetine (n = 107), and placebo (n = 112). Clinicians and patients were blind in both the fluoxetine-alone and placebo groups, and all knew that the combined and CBT-only groups involved active treatments. Assessments were made by blind independent evaluators, and outcome was measured by the Children's Depression Rating Scale and CGI-I.

Pharmacotherapy was manualized and monitored; it consisted of six sessions of 20 to 30 minutes spread over 12 weeks. Pharmacotherapists used a flexible dose of fluoxetine or placebo beginning at 10 mg, increasing to 20 mg after 1 week to a maximum dose of 40 mg by week 8. CBT consisted of 15 sessions of 50 to 60 minutes over 12 weeks with the adolescents alone, adolescents with parents and family, or parents alone. Beginning sessions (1 through 6) covered psychoeducation about depression, monitoring of mood, setting of goals, increasing participation in pleasurable activities, cognitive restructuring, and problem solving of social concerns. The second half of treatment focused on improving social skills (e.g., problems in social engagement, communication, negotiation, compromise, or assertiveness). Combined treatment was conducted by two clinicians, each following the manual for the treatment as conducted in monotherapy, but was integrated for partial response and dose increases.

Of the 439 participants who began the trial, 359 completed the 12 weeks of treatment, although the outcome data were based on the 351 participants who were assessed at the end of the treatment period (80% of the total). There were no significant differences among groups for dropouts or early terminators. There were no significant differences among the groups on any baseline characteristics, including demographics and illness severity. The sample was representative of the general depressed adolescent population in clinical practice, with a mean illness severity of moderate to severe.

Outcome results using the Children's Depression Rating Scale showed that combined treatment of fluoxetine and CBT was superior to placebo (p = 0.001) and to either monotherapy (p = 0.02 for fluoxetine alone and p = 0.01 for CBT alone). Fluoxetine alone was superior to CBT alone (p = 0.01). The completer response rate for combined treatment was 71% compared with 60.6% for fluoxetine alone, and 43.2% for CBT alone. The placebo response rate was 34.8%. The intent-to-treat analysis yielded the same findings: Combined treatment was superior to all other groups, and fluoxetine alone was superior to CBT alone. In this sample, CBT was not superior to placebo. However, the authors suggest that their sample may have been a more severely ill group both in MDD severity and in comorbidity, which may account for the poorer outcome in the CBT-alone group. The data from this study are consistent with findings on adult populations: Combined treatment is more effective than monotherapy in more severely depressed patients.

Maintenance Treatment

How long should therapy continue after an episode of MDD and what type of treatment best prevents relapse are important questions. Stangier and colleagues (2013) conducted a multicenter RCT to answer those questions. They compared a maintenance CBT and a manualized psychoeducation both combined with treatment as usual, which consisted of antidepressant medication, in 180 participants with remitted MDD. Inclusion for this study required current remission from *DSM-IV* MDD, HAM-D score of 9 or less, plus three or more past depressive episodes in adults between 18 and 65. Subjects were excluded if they were psychotic, suicidal, abusing substances, or medically unstable or had received CBT in the previous year. All participants were treated with maintenance antidepressant medication on an individual basis and doses were changed as needed. The experimental treatment included 8 months of either 16 50-minute sessions of CBT (weekly for several

months, gradually decreasing to monthly), or 20-minute manualized psychoeducation sessions.

The psychoeducation focused on symptoms and course of depression; the biopsychosocial model of etiology; medication side effects, complications, and compliance; signs of recurrence; and management of recurrence. Therapists were allowed to give advice, listened to patients' concerns, and reinforced patients' skills and resources but were not allowed to use any specific psychotherapeutic technique such as problem solving, cognitive restructuring, or skills training. CBT included cognitive case conceptualization, mindfulness meditation, cognitive restructuring, behavioral activation, and behavioral experiments.

Outcome (time to relapse) was measured using the Longitudinal Interval Follow-up Evaluation (LIFE). At the end of the 1-year follow-up period, 25.6% of participants dropped out (15 from the CBT group vs. 31 from the psychoeducation group, a significant difference). Although dropouts occurred during the treatment phase, 80% of the sample completed at least 12 sessions (n = 144); significantly more of the CBT group (n = 78) were completers. There were no differences between the two groups on demographic variables, nor were there significant differences in either time to relapse or risk status. What was significant was the number of previous episodes of MDD. Those who had five or more past episodes and received maintenance CBT (50%) relapsed less than those who received psychoeducation (73.2%), indicating a hazard ratio of 38% reduction in relapse risk. Participants with less than five episodes demonstrated no difference in relapse rate regardless of group. No other variables were significantly related to relapse. This study confirms that maintenance CBT protects against relapse in the most at-risk patients.

Frank and colleagues (1990) conducted a continuation treatment study of recurrently depressed patients aged 21 to 65 who had experienced at least three episodes of MDD, the prior episode lasting no longer than 2.5 years. Initially, 230 patients were treated with imipramine (150 to 300 mg) and weekly IPT for 12 weeks. For the next 8 weeks, patients were seen biweekly, then treated monthly until response was achieved (HRSD score of 7 or lower and a Raskin Severity of Depression score of at least 7). All patients continued in treatment for an additional 17 weeks at the same dosage (n = 157). To be entered into the maintenance protocol, patients were required to maintain a HRSD score of 7 or lower. Of the 230 who entered the acute treatment phase, 128 patients (30 males, 98 females) were randomized to one of five maintenance conditions—imipramine plus clinic visits (n = 28), IPT plus imipramine (n = 25), placebo plus clinic visits (n = 23), IPT alone (n = 26), and IPT plus placebo (n = 26), for 3 years.

The maintenance IPT involved monthly sessions conducted by a social worker, psychologist, or nurse practitioner. IPT therapists were highly trained and supervised by clinicians who had developed IPT (Bruce Rounsaville, Eve Chevron, Gerald Klerman, and Myrna Weissman). The imipramine dose averaged 200 mg and was administered by a psychiatrist who met with patients monthly. For those patients receiving placebo or IPT alone, medication was withdrawn over 3 weeks.

The attrition rate of the maintenance phase was 17% (n = 22), leaving 106 patients who completed the 3-year trial. Fifteen of the 22 dropped out due to noncompliance with the protocol, but only 4 reported side effects as the reason. The others who dropped out did so due to medical problems that interfered with continuation of treatment, moving out of the area, or other reasons.

The research showed that the likelihood of experiencing recurrence among those not receiving imipramine was great (OR = 4.9), whereas the likelihood of experiencing recurrence among those not receiving IPT was less (OR = 1.7) in the 3-year period following successful treatment of recurrent depression. Imipramine and clinic visits were as effective in preventing recurrence as combined imipramine and IPT, although both were more effective than IPT alone, IPT and placebo, and placebo with clinic visits. As a means of recurrence prevention, imipramine was the most effective treatment, more than combined treatment in this recurrently depressed sample. IPT alone had significant benefit in preventing recurrence.

Acute and Maintenance Treatment in the Elderly

Reynolds and colleagues (1996) reported on separate acute and continuation trials of combined therapy in elderly and midlife patients with recurrent MDD. The goal of these studies was to achieve the maximum number of remitted patients to be eligible for inclusion in an RCT of maintenance treatment. The first study involved 148 depressed patients aged 60 and over, considered the elderly group. During

the acute treatment phase, patients were treated with nortriptyline and weekly IPT modified for the needs of the elderly. Acute treatment lasted until the patient achieved a score of 10 or lower on the HRSD for 3 weeks, a remission score consistent with other studies of the elderly. The remission rate was 78.4% (n = 116). The number of dropouts was low, 12.2% (n = 18). After acute treatment, remitters entered continuation treatment for 16 weeks consisting of pharmacotherapy (same dose) and biweekly IPT to ensure complete remission and prevent relapse.

The midlife study included 214 recurrently depressed patients aged 21 to 59 (mean age, 38.5) who were treated with imipramine and IPT. Acute treatment in this group lasted until an HRSD score of 7 or lower was maintained for 3 weeks. The midlife remission rate was 69.6% (n = 149) with a dropout rate of 11.2% (n = 24). In the midlife group, remitters entered continuation treatment for 20 weeks, also consisting of same-dose pharmacotherapy and biweekly IPT. There were no significant differences in remission rates between the elderly and midlife groups for acute treatment.

The researchers analyzed the temporal course of response to treatment in both groups and found that the two groups were similar in that both showed a significant reduction in HRSD scores at 8 weeks. However, midlife patients experienced a faster reduction than the elderly patients.

There was a significant difference in relapse rates, with 15.5% of the elderly group (n = 18) and 6.7% of the midlife group (n = 10) relapsing while on combined treatment during the continuation phase. In addition, the elderly group experienced a shorter time to relapse than the midlife group (7.4 weeks in the elderly group and 16.6 weeks in the midlife group). Due to the uneven length of continuation treatment, the researchers reanalyzed the data, eliminating any midlife subjects who relapsed after the 16th week, and found that 3.4% (n = 5) of the midlife group relapsed during the first 16 weeks of continuation treatment. In comparison, 13.8% of the elderly group relapsed during the 16 weeks (n = 16), a significant difference. At the end of the study, 66.2% (n = 98) of the elderly patients and 57% (n = 122) of the midlife patients were eligible to enter the maintenance therapy condition. The maintenance data were not reported in this manuscript.

This study is included here even though it did not employ a monotherapy or placebo group because there are few data on outcomes using combined treatment with the elderly. In addition, there is value in comparing treatment results in the elderly with those in a younger population, especially one in which much research information has been collected.

Reynolds and colleagues (1999) conducted a maintenance trial on 187 recurrently depressed patients aged 59 or older. These patients were not demented, had a mean number of previous episodes of 5.3, and had no period of remission longer than 3 years.

Acute treatment included open-label nortriptyline combined with weekly IPT for 9 weeks (50% received some adjunctive pharmacotherapy). After the 9-week acute treatment period, those who were responders were continued on the combined nortriptyline and IPT treatment every other week for an additional 16 weeks to ensure stability of remission. Those able to sustain remission for 6 months were randomized for maintenance treatment. The 107 such patients were placed in one of four groups: monthly clinic visits with full-dose nortriptyline, placebo with clinical management, monthly maintenance IPT with pill placebo, and monthly maintenance IPT with nortriptyline. Maintenance therapy lasted for 3 years, but relapse or recurrence of MDD symptoms caused subjects to be dropped from the study.

Results of the maintenance trial showed that all active treatments were superior to placebo. The combined nortriptyline plus IPT was superior to IPT plus placebo, with a recurrence rate of only 20%. The combined treatment showed a trend toward significance (p = 0.06) over nortriptyline plus clinical management, with a 43% recurrence rate. The recurrence rate for IPT plus pill placebo was 64%, and the recurrence rate for pill placebo plus clinical management was 90%. The authors point out that 53% of the recurrences were associated with medication noncompliance. The strength of this study is the inclusion of a placebo arm. In addition, open-label treatment and the allowance of adjunctive medications make the results more generalizable to clinical practice.

Blackburn and Moore (1997) conducted both an acute and a maintenance treatment study of 75 recurrently depressed outpatients to determine whether cognitive therapy would be more effective than medication when used for maintenance treatment. Technically, this trial did not combine the two treatments at the same time. Rather, it used a crossover-type design, but it is included in this chapter because it is often cited and presents some important findings.

The MDD patients were randomized into one of three groups for 16 weeks of acute treatment followed by 2 years of maintenance treatment: antidepressants alone (n = 26), antidepressant first followed by cognitive therapy (n = 22), and cognitive therapy alone (n = 27). Medication treatment, conducted by general practitioners or psychiatrists, was determined by the clinician's choice, prescribed at or above the therapeutic dose and changed as needed. Meetings occurred once every 3 weeks for 30 minutes during acute treatment, but maintenance therapy meeting times were not mentioned. Cognitive therapy was conducted by trained clinicians weekly during the 16-week acute treatment and less frequently during maintenance (three sessions during month 1, two sessions during month 2, and once per month throughout the 2-year period).

Measures used were the HRSD and BDI. There were no significant differences between the three treatment groups on demographic variables, baseline HRSD and BDI measures, number of past depressive episodes, or number of hospitalizations or suicide attempts. The only significant difference was that the group that received antidepressants first followed by cognitive therapy had lower functioning prior to entering the study than the other two groups.

Thirteen patients were dropped from the acute phase analysis (11 who dropped out and 2 who received inadequate medication dosages). Of the 65 who completed acute treatment, there was significant improvement for all groups; 24% of the medication groups achieved remission, and 33% of the cognitive therapy group remitted. There was no difference among the three groups on HRSD scores. In addition, the authors analyzed whether depression severity accounted for any treatment differences in their sample and found that it did not, contrary to other findings.

After 24 months of maintenance treatment, although all patients continued to improve, there was no significant difference among the groups on either outcome measure. It should be noted that only 20 patients were assessed at 24 months. The relapse rates during the 2-year period were significant, with the cognitive-therapy-only group demonstrating the lowest rates (24%) compared with the medication-only group (31%) and the medication-first-then-cognitive-therapy group (36%). When the cognitive therapy maintenance groups were combined, the relapse rate was 26%, compared with 31% for the medication-only group.

We are including one more study that focused on the symptom of insomnia using CBT while treating the mood symptoms with escitalopram. This pilot RCT conducted at Stanford (Manber et al., 2008) recruited 30 individuals aged 18 to 75 with MDD and insomnia (defined as 2 consecutive weeks of at least 30 minutes of difficulty falling asleep and/or awakening after sleeping for three or more nights per week and less than 6.5 hours total sleep per night for three more nights per week). They excluded suicidality, psychosis, recent electroconvulsive therapy, seasonal affective disorder, past treatment with escitalopram, and having failed two SSRI treatments. No other sleep medication or treatment was allowed.

All participants were treated with escitalopram for 12 weeks (10 mg but up to 20 mg based on clinical response) in a standard protocol and randomly assigned to CBT-Insomnia (CBT-I) or a control treatment for seven sessions (five weekly, then two biweekly). CBT-I included an education component about normal sleep, circadian rhythms during depression, and effect of substances on sleep; sleep restriction and stimulus control instructions; stress, cognitive, and somatic arousal management as well as cognitive restructuring; sleep schedule adjustment; and relapse prevention. The control intervention included a quasi-desensitization procedure, education about sleep, and sleep hygiene, but no other intervention.

Depression was measured using HRSD and sleep was measured through diary and a recording device called an actigraph, which is the size of a watch. Results demonstrated significantly improved sleep in the CBT-I-plus-escitalopram group compared to the control-plus-escitalopram group. Remission of MDD was considered a score of less than 8 on the HRSD excluding the three sleep items, and the CBT-I group experienced 61.5% remission compared to 33.3% in the control group. However, this did not translate to a significant difference, probably because of small sample size. This pilot study suggests that augmenting antidepressant treatment with a psychosocial intervention for sleep in those with comorbid MDD and insomnia may be beneficial.

Summary

The main finding from these studies of treatment for depression is that combined treatment is superior to medication monotherapy when used to treat chronic

or severe major depression. Combined treatment is effective but not necessarily more effective than a stepped pharmacotherapy course. Relapse prevention is most effective when medication is combined with psychotherapy (CBT or IPT) for those who have had five or more episodes of MDD. Sequential treatment—adding an effective psychotherapy to medication treatment in those who did not previously respond to medication alone—has been shown to be efficacious. Patients with milder severity or a first episode of depression seem to benefit from either treatment alone at about the same rate, but one advantage of combining psychosocial treatment with medication may be in improved treatment adherence. Attrition rates are often higher in the medication-only groups (de Jonghe et al., 2001; Hautzinger et al., 1996); patients may drop out due to side effects or dissatisfaction with taking medication, although this is less frequent when medication is changed during the treatment course.

Most of the combined treatment studies that included an evidence-based treatment (CBT or IPT) used a tricyclic or a monoamine oxidase inhibitor rather than an SSRI, with the exception of the TADS trial in adolescents, which employed fluoxetine and CBT, with the result that combined treatment was more effective than monotherapy. It was suggested that the participants in the TADS were more severely ill, thus the higher response rate with combined treatment. Since SSRIs are more frequently prescribed in clinical practice, more RCTs using SSRIs in combination with CBT or IPT in MDD are needed.

In the primary care study (Mynors-Wallis et al., 2000), combined treatment did employ SSRI medication, but the psychosocial treatment chosen was problem-solving therapy, not CBT or IPT. The problem-solving therapy was not well received by patients (highest attrition rate), nor has it been demonstrated as particularly effective. In this study, combined treatment was no more effective than medication alone or the problem-solving therapy alone.

One last issue to consider when evaluating the results of clinical trials for MDD that use the HRSD as the primary outcome measure is rater training and reliability testing. Some of the older studies did not describe training of raters, and reliability tests were not mentioned. The HRSD, in its original format, has very few probes for each item, leaving it to the interviewer to know what to ask in order to rate the item. Frequently, independent raters are not highly experienced clinicians and are not necessarily familiar with scoring guidelines and rules of administration (Lipsitz et al., 2004). Williams (1988) developed the Structured Interview Guide for Hamilton Depression Scale (SIGH-D), where gate and follow-up questions are provided so that interviewers systematically gather the same material over time, increasing the reliability of the data. Use of such structured guides and attention to rater training could significantly affect the results of treatment trials (Lipsitz et al., 2004).

PANIC DISORDER

There have been many RCTs of treatments for PD, but almost all have compared medication alone to psychotherapy alone, and both to placebo; little has been conducted on combined treatment.

The gold-standard RCT for PD was a multicenter study conducted by Barlow, Gorman, Shear, and Woods (2000). This four-site study (Boston, New York, Pittsburgh, and New Haven) compared imipramine plus medical management, CBT alone, their combination, placebo plus CBT, and placebo plus clinical management in the treatment of 312 patients with PD. There were three phases to the study: acute treatment, maintenance treatment, and follow-up.

All patients met criteria for PD using the Anxiety Disorders Interview Schedule Revised and had experienced at least one full or limited panic attack in the 2 weeks prior to starting treatment. Most Axis I disorders were excluded except major depression, and some agoraphobia (mild) was acceptable. After passing the screening procedures, 326 PD patients without agoraphobia were randomized to one of the five acute treatment groups: CBT alone (n = 77), imipramine alone (n = 83), placebo alone (n = 24), CBT plus imipramine (n = 65), or CBT plus placebo (n = 63).

In the acute phase, patients were seen weekly for 12 weeks. The CBT used in this study is called Panic Control Therapy, developed by Barlow and Craske, and focuses on psychoeducation, breathing retraining, relaxation exercises, cognitive restructuring, interoceptive exposure (exposure to bodily sensations that are similar to those experienced during a panic attack), and situational exposure. Imipramine and placebo were both double-blind administered in a fixed, flexible dose beginning at 10 mg titrated by 10 mg up to 50 mg in 4 to 5 days, then increasing more

rapidly to 200 mg by week 5, with a maximum dose of 300 mg. Medical management involved monitoring adverse effects, clinical state, and symptoms with a goal of increased compliance with medication use. It should be noted that patients were allowed some benzodiazepine use through the acute treatment phase.

Those administering CBT and pharmacotherapy were well trained, experienced clinicians, and each conducted treatment according to a manual, with adherence monitored regularly. All assessments were conducted by independent evaluators. Primary outcome measures included Panic Disorder Severity Scale (PDSS), a seven-item, clinician-administered scale that measures panic frequency, severity, anticipatory anxiety, avoidance, and impairment; and the CGI-I. Response was calculated by a 40% decrease in PDSS score from baseline and a CGI-I of 1 or 2 (much improved).

Ninety-nine participants dropped out after randomization, with no significant difference in attrition rates among the five groups. At the end of the acute phase, all four treatment groups were superior to placebo but not different from each other. Improvement was faster for patients treated with medication. The PDSS response rate for those who completed treatment in the imipramine group was 74.5%, whereas the CBT-only group's response rate was 67.3%. The imipramine-plus-CBT group had a response rate of 84.4%, and the CBT-plus-placebo group's response rate was 80%. The placebo-only group's response rate was 38.5%. Using an intent-to-treat analysis, the PDSS response rates for the five groups were as follows: CBT alone 48.7%, imipramine alone 45.8%, CBT plus imipramine 60.3%, CBT plus placebo 57.1%, and placebo alone 21.7%. There was no evidence that combination therapy was better than monotherapy.

In the maintenance phase, responders to acute therapy (including placebo responders) were continued on the original treatment assigned, still under blinded conditions, and seen monthly for the next 6 months ($N = 170$). Imipramine- and placebo-treated patients continued on medication, and CBT-treated patients were given monthly booster sessions. The results showed that placebo-treated patients who had responded to placebo during acute treatment had a poor outcome during the maintenance phase. Patients assigned to CBT alone, imipramine alone, and combination therapy continued to be responders. The maintenance-phase PDSS response rates by group were as follows for completers: CBT alone 73.2%, imipramine alone 79.5%, CBT plus imipramine 90%, CBT plus placebo 76.3%, and placebo only 37.5%. The intent-to-treat PDSS response rates were CBT alone 39.5%, imipramine alone 37.8%, CBT plus imipramine 57.1%, CBT plus placebo 46.8%, and placebo only 13%.

In this phase combined treatment was significantly better than monotherapy. The PDSS response rate was significantly higher in the combined group when compared with each individual treatment (CBT plus imipramine vs. CBT, $p = 0.04$; CBT plus imipramine vs. imipramine, $p = 0.03$).

The last phase of this study was the follow-up phase, lasting 6 months after treatment was completed. The number of patients who were assessed during follow-up was 116. The PDSS completer response rate was 85.2% for the CBT-only group, 60% for the imipramine-only group, 50% for the CBT-plus-imipramine group, 83.3% for the CBT-plus-placebo group, and 100% for the placebo-alone group (there were only three participants in the placebo group after this phase). The intent-to-treat response rates were CBT only 32.4%, imipramine only 19.7%, CBT plus imipramine 25%, CBT plus placebo 41%, and placebo only 9.1%. The CBT-without-imipramine groups had fewer patients relapse than the imipramine-alone and combined treatment groups.

This study demonstrates the effectiveness of imipramine, CBT, and their combination for acute treatment of PD. Medication (imipramine) works more quickly than CBT but is not tolerated as well, and at the end of treatment, both are quite effective. The combined treatment was not as durable as CBT alone in the follow-up period; in fact, the relapse rates were about the same as for imipramine alone. The authors concluded that in the long term medication may interfere with CBT efficacy.

Another RCT involving combined treatment for PD was conducted by de Beurs, van Balkom, Lange, Koele, and van Dyck (1995) in Amsterdam comparing fluvoxamine and exposure therapy, monotherapy, and placebo in PD with agoraphobia. After screening for panic disorder using the Anxiety Disorders Interview Schedule, 96 PD patients with moderate or severe agoraphobia, who were between the ages of 18 and 65, were medically healthy, and did not have any history of psychosis, organic mental disorder, or substance use disorder, were randomized to one of four treatment groups ($n = 24$ per group). All psychoactive

medications except benzodiazepines were discontinued before subjects entered the protocol.

The four treatment groups were fluvoxamine plus exposure therapy, placebo plus exposure therapy, psychological panic management plus exposure therapy, and exposure therapy alone. The fluvoxamine and placebo treatments began at 50 mg, administered by a psychiatrist or psychiatric resident over 12 weekly sessions, and were titrated to 100 mg in week 2 and 150 mg in week 3. Patients were told about the effects of fluvoxamine and the serotonergic pathways in the brain of PD patients. Their medication dose was kept stable at 150 mg unless side effects necessitated a reduction. No exposure therapy was conducted until after 6 weeks of medication treatment, and patients were told to avoid exposing themselves to feared situations until the medication started working.

Psychological panic management was conducted by clinicians experienced in behavior therapy. Sessions were held weekly and focused on psychoeducation about panic, the hyperventilation process (its role in panic attacks), and the cognitive process whereby bodily sensations provoke fear thoughts and fear thoughts further provoke bodily sensations. Patients were then encouraged to bring on panic-like sensations by hyperventilation, first in the session and then later at home. Patients were trained to breathe into a paper bag to counteract the hyperventilation process and later to breathe from the abdomen.

The exposure therapy (in vivo) began after 6 weeks of treatment (fluvoxamine, placebo, or panic management). The therapists conducting exposure therapy were the same as the panic management therapists. Patients were told to practice their techniques (those in panic management) in situations that they feared or avoided and were encouraged to gradually expose themselves to those situations. During the sessions they constructed a hierarchy of agoraphobic situations. Homework was then assigned to practice going into those situations for at least 90 minutes, three times per week.

Measures were self-report scales including the Fear Questionnaire (FQ), the Mobility Inventory (MI), the Agoraphobia Cognitions Questionnaire, the Bodily Sensations Questionnaire, the SCL-90, the BDI, and the Depression Adjective Checklist. The authors created a composite score from subscales of these instruments that measure the same construct. The agoraphobia composite score combined the agoraphobia subscales of the FQ, the SCL-90, and the MI avoidance when alone scale. The composite for depression combined the BDI, the Depression Adjective Checklist, and the SCL-90. The last composite score measured bodily sensations and combined the Bodily Sensations Questionnaire and a subscale of the Agoraphobia Cognitions Questionnaire. All composite scores ranged from 1 to 10, with the higher score reflective of more symptomatology.

All patients underwent a behavioral avoidance test that included three tasks: walking 3 miles from the clinic toward town, supermarket shopping, and riding on a crowded streetcar, for a short period of time. Evaluations of the patients' ability to perform the tasks and the amount of anxiety experienced during the tasks were rated and averaged to yield one score from 1 to 10, with the higher score indicating poor performance.

Before being assigned to a treatment group, each patient was interviewed by an independent evaluator who devised four treatment goals for the patient. Using a 5-point scale, these goals were reformulated into a goal attainment scale and became another measure of treatment outcome. During the treatment, patients were asked to monitor their panic attacks on a registration form.

Of the 96 patients who began treatment, only 76 completed the full course. Six patients dropped out due to treatment-related problems and six due to other reasons. There were no significant differences between the dropouts and the completers.

The authors tested whether blindness or the use of benzodiazepines affected the results, and neither was found to be significant. All treatment groups experienced significant improvement on the three composite scores from baseline to end of treatment. The fluvoxamine-plus-exposure group experienced superior effects compared with the other three groups. There were no significant differences among the placebo-plus-exposure group, the psychological-panic-management-plus-exposure group, and the exposure-alone group. On the behavioral avoidance test, all patients experienced significant improvement on performance after treatment. The intent-to-treat analysis did not yield different results from the completer analysis.

Using the panic attack registers, the researchers analyzed panic-free status as well as increase in panic in the four groups over time. The participants in the psychological panic management group had poorer

outcome than the other three groups, who were not different from each other.

Effect sizes for the four groups on each composite score were calculated. For agoraphobia, fluvoxamine plus exposure was 2.00, placebo plus exposure was 1.29, psychological panic management plus exposure was 0.99, and exposure alone was 1.32. For depression, fluvoxamine plus exposure was 1.28, placebo plus exposure was 0.75, psychological panic management plus exposure was 0.24, and exposure alone was 0.66. For bodily sensations, fluvoxamine plus exposure was 1.22, placebo plus exposure was 0.82, psychological panic management plus exposure was 0.73, and exposure alone was 0.75.

The conclusion drawn from this study is that combined treatment of fluvoxamine plus exposure therapy was more effective than exposure alone (with or without placebo). The psychological panic management was not very effective in decreasing panic attacks. This is not surprising, since breathing retraining alone is not very effective in preventing panic attacks (Schmidt et al., 2000). It is important to note that this study did not measure response with a particular criteria set, such as CGI, making the data difficult to compare with those from other trials. Combined treatment may have been superior to the other treatments, but not all patients were panic-free.

Loerch and colleagues (1999) used moclobemide and CBT to treat patients with PD with agoraphobia for 8 weeks. They randomized 55 patients to three conditions: placebo plus CBT, moclobemide plus clinical management (psychological placebo), and placebo plus clinical management. In this trial, moclobemide plus clinical management was not more effective than placebo, so it is not surprising that the combination of moclobemide and CBT was not superior to CBT plus placebo.

A study of combined medication and CBT for PD in primary care was conducted by Roy-Byrne and colleagues (2005) in six academic medical centers in Seattle, San Diego, and Los Angeles. The Collaborative Care for Anxiety and Panic study aimed to determine whether evidence-based treatments could be generalized to primary care. Patients met study criteria if they had PD and had experienced a panic attack in the week prior to study entry, spoke English, and were willing to take medication in addition to receiving CBT treatment. After intensive screening procedures (diagnostic evaluation was determined by use of the Composite International Diagnostic Interview), 232 panic patients were enrolled and randomly assigned to the intervention group (n = 119) or usual care (n = 113).

The intervention consisted of six sessions of CBT in person over a 3-month period and six telephone contacts lasting between 15 and 30 minutes every 6 to 12 weeks over the next year. The CBT was conducted by the "behavioral health specialist" (a master's-level or recent doctoral-level individual with little previous CBT experience). An instructional videotape explaining about PD and the treatment was also given to patients. Medication was administered by the primary care physician (PCP) under the supervision of a psychiatrist. The PCPs had received an hour-long didactic training on medication treatment for panic. SSRIs were given first if there was no history of two previous failed trials; otherwise the PCP could choose a different antidepressant such as a tricyclic, nefazodone, or mirtazapine for 6 weeks. Clinical care was managed by the behavioral health specialist who was in contact with the PCP regularly via telephone, fax, or e-mail.

Measures included diagnostic assessment (Composite International Diagnostic Interview), panic frequency and severity, agoraphobic avoidance, other fears and anxiety using the FQ, the Anxiety Sensitivity Index (ASI), and assessment of pharmacological and psychotherapeutic help received (amount and type), all administered at baseline and every 3 months throughout participation in the study. Outcome was measured by a subscale of the World Health Organization Disability Scale, the Global Physical and Mental Health Scale short form (SF-12), the Center for Epidemiologic Studies-Depression Scale, and ASI. Response criteria or "high end-state functioning" was based on a composite score of the above measures: no panic attacks in the previous month, minimal anticipatory anxiety about having a panic attack (one or less on a 0- to 3-point scale), and a score of less than 10 on an agoraphobia subscale.

There were no significant differences between the two treatment groups at baseline. The sample was primarily female (67%), with a mean age of 41.2, mostly educated (76% graduated high school, 39% had some college or more) and predominantly Caucasian (65.5%; Hispanic, 13%; African American, 13.8%). Comorbidity of a medical condition occurred in almost two thirds of the sample; 55.6% had comorbid MDD, 45.7% had GAD, 29.3% had PTSD, and 39.7% had SAD. Very few had received two or more sessions of CBT-type treatment previously (3.5%), and

only 28% had received any antipanic medication for at least 6 weeks before entering the trial.

Of those who were assigned to the CBT intervention group ($N = 119$), 81 (68%) received four to six sessions of CBT, 24 (20.1%) received one to three sessions, and 14 (11.8%) received no sessions. Adherence to the treatment was measured by independent clinical raters employing the same method as used in Barlow and colleagues' multicenter study (2000), resulting in adequate adherence to the treatment manual. The study investigators were concerned that a "spillover" effect might occur. Since some PCPs had patients in the intervention group and others in usual care, they might use the knowledge gained from the intervention training to influence their treatment in usual care. However, there were no differences found between the PCPs who had patients in both groups and the PCPs who had patients only in the usual care group.

Attrition from the study was as follows: At the 3-month assessment only 1 participant had dropped out (from the intervention group); at the 6-month assessment there were 2 dropouts from the usual care group and 8 dropouts from the intervention group; at the 9-month follow-up there were 4 dropouts from the usual care group and 10 dropouts from the intervention group; and at the final 12-month follow-up assessment there were 5 dropouts from the usual care group and 11 dropouts from the intervention group.

Although 6 months of CBT treatment (consisting of six sessions encompassing all seven techniques) was offered to the intervention group, only 63% actually received three or more sessions consisting of four of the seven techniques at the 3-month assessment and only 17% at the 6-month assessment. In the usual treatment group, 14% had received three or more sessions consisting of four of seven techniques at the 3-month assessment, and 9% had at the 6-month assessment, a highly significant difference between groups in the amount of CBT received. At the 9-month assessment, there was no difference between the groups, but significance was found at the 12-month assessment period, with 6% of the intervention group and 11% of the usual care group having received three or more sessions of four of seven CBT techniques.

In the intervention group, 44% actually received appropriate antipanic medication at the 3-month assessment, and 40% of the usual care group received appropriate antipanic medication. The number of participants who actually received appropriate antipanic medication throughout the follow-up period was about the same for both groups: 42% at 6 months, 41% at 9 months, and 41% at 12 months in the intervention group; and 39% at 6 months, 39% at 9 months, and 39% at 12 months in the usual care group.

The difference between the two groups becomes clear when looking at high end-state functioning as the outcome. The intervention group demonstrated a superior proportion of patients who achieved high end-state functioning at all assessment points. At the 3-month assessment, 20% of the intervention group was considered remitted, whereas only 12% of the usual care group remitted. At the 12-month assessment, 29% of the intervention group and 16% of the usual care group were responders. Using the ASI as the outcome measure, 66% of the intervention group versus 38% of the usual care group were responders at the 12-month assessment period. The study showed trends toward significance in dose response for both CBT and antipanic medication. Those who received at least four CBT technique components while attending at least six sessions showed a better response than those who received at least four CBT components while attending three to five sessions (56% vs. 40%). Those who took appropriate medication for 3 months showed a better response than those who took appropriate medication for 6 to 11 weeks (35% vs. 29%). The power was limited in these analyses, contributing to the lack of significance.

One other measure of importance showed significant improvement between the two groups. At all assessment points, the usual care group demonstrated more improvement in depression (23%) than the intervention group (19%).

In this trial, conducted in the primary care setting, the combination of CBT and medication delivered by PCPs and behavior specialists was superior to usual care in achieving high end-state functioning and response in PD patients. Since the medication component of the treatment did not differ between the two groups, the CBT treatment accounts for most of the added improvement experienced by the patients. Only 40% of the intervention group actually completed the entire course of CBT, whereas 72% in Barlow and colleagues' (2000) trial completed 11 sessions of CBT. This study did not exclude subjects who failed to continue treatment, as usually is the case in clinical trials. There was no placebo group for comparison of the efficacy of combined treatment, but

the utility of including this trial here is to demonstrate treatment effectiveness in the primary care setting.

The only other combined treatment RCT in PD was conducted by Marks and colleagues (1993) in London and Toronto using alprazolam, placebo, situational exposure, and relaxation therapy. The 154 panic patients were randomly assigned to one of four groups: alprazolam plus situational exposure (considered the combined treatment group, $n = 40$), alprazolam plus relaxation therapy (considered a medication plus psychological placebo, $n = 37$), placebo plus situational exposure (considered placebo plus psychological treatment, $n = 38$), and placebo plus relaxation therapy (considered a double placebo, $n = 39$).

All participants were screened using the SCID for *DSM-III;* they were adults between the ages of 18 and 65 who had PD, had experienced some attacks in the previous 4 weeks, did not have other Axis I disorders, and were not on any medication when entered into the protocol. In addition, patients underwent a physical examination and laboratory tests to determine medical status.

For the medication groups, the beginning dose of alprazolam was 1 mg, then titrated to a maximum dose of 10 mg, with a mean dose of 6 mg. All patients before randomization met with an evaluator who assessed which situations were feared and/or avoided. The exposure therapy involved first reading a chapter from the manual *Living With Fear.* With the therapist, the patient planned exposures to situations that had been listed with the evaluator. The therapist accompanied the patient for the first two sessions. During the exposures, the patient rated his or her level of anxiety every 30 minutes of the two exercises. The relaxation therapy involved giving patients audiotapes of instructions to be used at home for 1 hour daily. During sessions, the therapist reviewed the patients' weekly diaries and checked progress. No instructions for exposure were given, and patients were told to "do whatever you wish" if they asked about exposure. All treatment lasted for 8 weeks.

Measures for outcome were ratings on the phobia list (0 to 8) by the patient and the independent evaluator, Phobia Questionnaire (PQ), Attack and Anticipatory Anxiety Scale, HRSD, BDI, and CGI-I. Ratings occurred at baseline, 4 weeks, and 8 weeks (posttreatment), and at 43 weeks for follow-up.

There were no significant differences among the four groups at baseline and no differences between the two sites, so all the results were pooled. Results for the alprazolam groups showed that patients improved during the first 4 weeks on a measure of panic attack frequency but remained steady until week 8. The exposure groups improved by week 2 and continued to steadily improve until week 8. Using the CGI data at 8 weeks, the percentage of patients who were considered improved (rating of 1 or 2) by group were 71% in the alprazolam-plus-exposure group, 71% in the placebo-plus-exposure group, 51% in the alprazolam-plus-relaxation group, and 25% in the placebo-plus-relaxation group. After medication taper, only 36% of the alprazolam-plus-exposure group, 29% of the alprazolam-plus-relaxation group, and 18% of the placebo-plus-relaxation group stayed well, and 62% of the placebo-plus-exposure group stayed well.

The combination treatment was only slightly better than the other treatments at the end of the 8 weeks. The alprazolam groups relapsed more frequently than the exposure therapy group, so that exposure alone was the most effective treatment after medication was discontinued. Some of the difficulty in this trial with relapse after medication discontinuation may be attributed to the very rapid withdrawal of alprazolam, which may have produced severe withdrawal symptoms in the patients.

In summary, there is no advantage to combined treatment in PD. The use of imipramine combined with CBT is no more effective than imipramine alone. The combination of a benzodiazepine and CBT is also no more effective than either treatment alone and may even be relatively contraindicated, with data suggesting poor long-term outcome when compared to CBT alone.

OBSESSIVE-COMPULSIVE DISORDER

The growing research literature on the combined treatment of pharmacotherapy and psychotherapy for the treatment of OCD lends itself nicely to being grouped into three main categories: acute treatment, long-term outcome/maintenance, and treatment discontinuation. Combination treatment studies are included when delivered concomitantly as well as sequentially.

Acute Concomitant Combined Treatment

Foa and colleagues (2005) conducted a randomized, placebo-controlled trial comparing clomipramine,

exposure and response prevention, and their combination in the treatment of OCD. Patients were randomized to one of four conditions: clomipramine alone ($n = 47$), exposure and response (ritual) prevention alone ($n = 37$), exposure and response prevention plus clomipramine ($n = 33$), and pill placebo ($n = 32$). The exposure sessions were 2 hours daily for the first 3 weeks, followed by 45-minute sessions weekly for 8 weeks. In the clomipramine-alone group, the mean dose at the end of the study was 196 mg (SD 82) for those subjects who completed at least one therapy session and 235 mg (SD 23) for those who completed the trial. In the clomipramine-plus-placebo group, the mean dose was 163 mg (SD 65), or 194 mg (SD 48) when only counting those who completed the study.

After 12 weeks, the results showed that exposure and response prevention were superior to clomipramine and to pill placebo on all measures. Addition of clomipramine to exposure and response prevention did not improve outcomes. The authors suggest that the combination treatment may have failed to show superiority to the exposure and response prevention alone group because the intensive phase of exposure and response prevention (the first 3 weeks of the study) was over by the time the clomipramine would have generated an effect. The exposure and response prevention was so successful it may have left little room for further improvement by the addition of clomipramine.

Cottraux and colleagues (1990) compared the combinations of fluvoxamine plus exposure therapy, pill placebo plus exposure therapy, and fluvoxamine with antiexposure therapy. There was no pill placebo-plus-antiexposure group, which was considered to be an unethical control group. Twenty patients were randomized to each of the three groups. The fluvoxamine-plus-antiexposure group was single-blind; the other two groups were double-blind. Over this 24-week study, patients met with the psychiatrist nine times. Patients were permitted "occasional use" of the benzodiazepine bromazepam. Exposure sessions consisted of 8 weeks of exposure homework assignments, followed by 16 weeks of guided exposure and response prevention. The sessions were not standardized and for some patients included couples counseling, cognitive restructuring, and/or assertiveness training. Antiexposure instructions involved avoiding fearful stimuli and engaging in ritualized behaviors to relieve anxiety.

Results showed that all three groups improved on measures of rituals and depression, at weeks 24 and 48. There was a small but nonsignificant superiority for combined treatment up to week 24. The sample size in each group was somewhat small, and there is no indication that an intent-to-treat analysis was used. The high baseline levels of depression, the possible confounding use of a benzodiazepine, the loosely standardized exposure therapy sessions, and the very high noncompliance rate in the antiexposure group make it difficult to draw conclusions from this study. However, the data do not seem to point toward superiority for combined treatment.

As D-cycloserine (DCS) has showed promise in other disorders, it has been studied in OCD with somewhat mixed results. DCS is a partial agonist at the *N*-methyl-D-aspartate glutamate receptor (NMDAR) that has been effective in treating other anxiety disorders that involve exposure-based treatments.

Kushner and colleagues (2007) looked at adding DCS to exposure and response prevention. A total of 32 participants enrolled in the study and completed at least one exposure and response prevention session. Twenty-five completed the study. Psychiatric medications were continued if the dose had been stable 2 months prior to study entry, and those with hoarding or ordering as their primary ritual were excluded. All subjects underwent 10 sessions of twice-weekly exposure and response prevention and were randomized to either 125 mg DCS or placebo to be taken 2 hours prior to psychotherapy. Although at the end of the study there were no between-group differences, the authors point out that the DCS group tended to improve faster and had more study completers.

Storch and colleagues (2007) enrolled 24 participants and randomized them to exposure and response prevention plus DCS taken 250 mg 4 hours prior to psychotherapy or placebo. Subjects were allowed to continue psychotropic medications as long as the doses were stable 12 weeks prior to study entry. Similar to the results of the Kushner study, no overall differences were found between the groups, but there was a trend toward a lower symptom burden in the DCS group in weeks 4 to 6 of this 12-week study.

Wilhelm and colleagues (2008) randomized 23 subjects on stable medication doses to 10 twice-weekly exposure and response prevention sessions plus DCS 100 mg or placebo given 1 hour prior to the session.

A similar conclusion was drawn here: The DCS group had lower OCD symptoms scores at the middle of treatment but not at the end of the study. The authors point out that DCS may, in fact, be quite helpful in the treatment of OCD because the faster response rate may decrease the number of treatment dropouts. Chasson and colleagues (2010) looked at the slope of change in the Wilhelm study and concluded that the subjects in the DCS group got better 2.3 times faster than the placebo group.

Overall, DCS shows some promise in the treatment of OCD, particularly in that it appears to decrease the time to symptomatic improvement when combined with exposure and response prevention. Still, the studies conducted have been small and few. More research is required in this area before firm conclusions can be drawn.

Acute Sequentially Combined Treatment

Van Balkom and colleagues (1998) examined the sequential combination of fluvoxamine with CBT in the treatment of OCD, compared with CBT alone. Patients were randomized to one of five groups: cognitive therapy alone, exposure and response prevention alone, 8 weeks of fluvoxamine followed by 8 weeks of cognitive therapy, 8 weeks of fluvoxamine followed by 8 weeks of exposure and response prevention, or a waitlist control for 8 weeks. At 8 weeks, both the cognitive therapy and the exposure and response prevention groups did significantly better than the waitlist control group. At week 16, the sequential combination of fluvoxamine plus exposure and response prevention did not show any significant difference from the CBT-alone treatments on all measures. The same results were obtained with an intent-to-treat analysis of the data.

The participants in this study were not blind to their respective groups at randomization, which may have influenced their outcome. One possible explanation for the combination groups' failure to demonstrate better outcome than the CBT-alone groups may be due to the combination groups' having received 8 weeks less CBT than did the CBT-alone groups. Since there was no fluvoxamine-alone group, this study does not allow us to make inferences about the efficacy of combination treatment compared with fluvoxamine alone.

Hohagen and colleagues (1998) studied the interaction of CBT plus fluvoxamine compared with CBT plus placebo. They also looked at treatment outcome of OCD symptoms after treatment of secondary depressive symptoms. In this multicenter study conducted in Germany, 60 patients were randomized to receive CBT plus fluvoxamine or CBT plus placebo. Because the groups differed significantly in terms of baseline symptom severity, outliers were dropped, and the sample was reduced to 49 patients. In this study, participants received either fluvoxamine or placebo for 3 weeks, followed by CBT during weeks 4 to 8.

Both groups showed significant response. Obsessions but not compulsions were significantly reduced in those receiving CBT plus fluvoxamine, as compared with CBT plus pill placebo. However, no significant differences were noted with regard to compulsions. The lack of therapeutic efficacy in treating compulsions with CBT in this study may reflect the techniques used. We now know that although often difficult to treat, obsessions are amenable to a variety of techniques in the CBT armamentarium. The treatment of OCD symptoms in patients who had comorbid depression was enhanced by the addition of fluvoxamine to CBT.

There have been several small and uncontrolled trials examining the addition of either psychotherapy to medication or vice versa in subjects who did not respond to the initial intervention. Simpson, Gorfinkle, and Liebowitz (1999) added exposure and response prevention to six out of seven eligible patients who had not responded to an adequate dose of an SSRI after 12 weeks of treatment and found that all six responded, with a mean decrease on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) of 49%, despite the fact that only five completed the study.

Kampman and colleagues (2002) added 12 weeks of CBT in 14 patients drawn from a pool of 56 initially enrolled in a study examining the effectiveness of fluoxetine in OCD. Patients who had not responded to 12 weeks of fluoxetine were eligible for the CBT phase of the study. Nine participants completed the 12 weeks of CBT, and seven of the nine had a large reduction in symptoms (mean decrease in Y-BOCS 41%). Again, the results are promising for the addition of CBT to SSRI nonresponders, but it is difficult to draw conclusions from such a small and uncontrolled trial.

Tolin and colleagues (2004) examined a sample they determined to be a medication-refractory (failure of at least two adequate SRI trials) and clinically challenging sample (having a comorbid Axis

I or Axis II diagnosis). Participants were enrolled in a waitlist-controlled open trial. The authors indicate that the participants were required to be on stable doses of medications for at least 2 months prior to study entry and were continued on these medications throughout the study. Individuals with bipolar disorder, pervasive developmental disorder, mental retardation, psychotic disorder, current substance use disorder, or serious suicidal or homicidal ideation were excluded from the study. Patients enrolled were initially put on a 1-month waiting list and then underwent 15 psychotherapy sessions, which could be administered anywhere from one to five times weekly. There were a total of 15 completers.

As measured by the Y-BOCS, there was a 29.6% reduction of symptoms in intent-to-treat analysis. The gains, however, did decrease over time; compared to baseline there was a 26.64%, 23.36%, and 22.65% decrease in symptoms at 1, 3, and 6 months after treatment, respectively. The authors argue that although symptoms had increased at the 6-month follow-up, overall symptom burden still tended to be lower than it had been at study entry. There remains a possibility that treatment response could continue to decline over time, but the study's follow-up was limited to 6 months.

Tundo and colleagues (2007) enrolled 36 subjects who were nonresponders to at least one adequate SRI trial in a naturalistic study. Subjects were continued on current medications and were assigned to CBT, the course of which was determined by individual therapists and subjects both in terms of contact frequency and number of sessions. Overall, 28 completed 6 months of follow-up and 25 completed 1 year of follow-up, with a mean Y-BOCS reduction of 19%, which was statistically significant. The authors point out that the results are generally consistent with the studies by Simpson and colleagues (1999), Kampman and colleagues (2002), and Tolin and colleagues (2004) in that CBT supplementation appeared successful in patients who had not responded to medications. However, the mean reduction in symptoms was less than in the previous studies, with a smaller percentage of improved patients (present study 42%, Simpson et al. 86%, Kampman et al. 77%, Tolin et al. 66%); the authors argue that their sample consisted of patients who had generally failed more medication trials and had higher baseline Y-BOCS scores (28.2 in present study, 23.8 in Simpson et al., 25.7 in Kampman et al., and 25.1 in Tolin et al.), resulting in decreased treatment effectiveness.

Tenneiji and colleagues (2005) examined the addition of psychotherapy to paroxetine and venlafaxine in 96 participants with OCD (from a total of 150) who had a partial response to medication in a double-blind trial. Those who had at least a 25% reduction in symptoms as measured by the Y-BOCS after 3 months of drug treatment were given the option of randomization to continuing drug treatment alone or drug treatment plus behavior therapy for an additional 6 months. The dropout rate was higher in the combination group than in the drug-alone group (30% and 6% respectively); however, 53% in the combination group were judged to be in remission at the end of the study as opposed to 11% in the drug-alone group. The authors argue that although the differential dropout rate could be considered a weakness of the study, it is similar to the dropout rate observed in other trials of behavioral therapy, and that a high dropout rate is expected in a real-life clinical setting.

Simpson and colleagues (2013) enrolled subjects who remained symptomatic after 12 weeks of an adequate SRI trial. Participants were randomized to addition of exposure and response prevention, risperidone, or placebo and were continued on their current SRI as well as other psychotropic medications at stable doses, except for antipsychotics. Eighty-six of the 100 patients enrolled completed the studies. The authors concluded that exposure and response prevention was superior to both risperidone and placebo; although risperidone was numerically better than placebo, the difference was not statistically significant.

Overall, this group of studies suggests that there is unlikely to be great benefit to combined treatment, except in those who have failed to adequately respond to psychotherapy or medication. It is important to note, however, that many of the studies described that have looked at this population are not controlled trials, and therefore further research is necessary to elucidate this point.

Long-Term Outcome

There is a dearth of data investigating the long-term outcome of combined pharmacology and psychotherapy for the treatment of OCD. The available studies have been uncontrolled and naturalistic in design, with relatively small sample sizes, but they still provide valuable insight.

The results of naturalistic 6-month and 5-year follow-ups, with pooled data from van Balkom and colleagues' (1998) RCT and from another psychotherapy-only RCT (van Oppen et al., 1995) comparing cognitive therapy with exposure-based therapy and fluvoxamine, were published by de Haan and colleagues (1997) and van Oppen, van Balkom, de Haan, and van Dyck (2005), respectively. The two original studies, from which the data were pooled, used the same inclusion and exclusion criteria and identical treatment protocols, therapists, clinics, assessment methods, and measurement intervals.

Results of the 6-month follow-up showed that 17 of the 45 nonresponders in the original studies became responders. The 5-year follow-up showed no significant difference in clinical outcome among the cognitive therapy, exposure with response prevention, and fluvoxamine in combination with the CBT groups.

It is important to note that, as naturalistic studies, there were no control conditions for the treatments during the follow-up periods, and most of the patients who responded by 6 months had received further treatment after the initial study period.

O'Sullivan and colleagues (1991) conducted a 6-year follow-up of 34 of 40 subjects who had received 3 or 6 weeks of exposure therapy and clomipramine or placebo for 36 weeks. They found that there was no difference between the clomipramine and placebo groups but that outcomes were improved with longer duration of psychotherapy. Rufer and colleagues (2004) followed 30 subjects 6 to 8 years after an initial study of 37 inpatients randomized to CBT plus fluvoxamine or placebo. Again, combination therapy was found to be no better than CBT alone.

Cottraux, Mollard, Bouvard, and Marks (1993) conducted a 1-year naturalistic follow-up of Cottraux and colleagues' (1990) RCT discussed above. Fifty-five percent of the patients who began the initial study were available for testing at the 1-year follow-up period. The results suggest that all patients, regardless of treatment, were improved at the 1-year follow-up; however, those who received exposure therapy were less likely to have reported antidepressant treatment.

Treatment Discontinuation

Few studies have examined the effects of treatment discontinuation in those who have responded to OCD treatment. Simpson and colleagues (2004) published data from the discontinuation phase of Foa and colleagues' (2005) RCT, discussed above, which compared exposure with response prevention, clomipramine, their combination, and pill placebo. Those who were treatment responders in the acute phase were eligible to enter the discontinuation phase.

During the discontinuation phase, which lasted 12 weeks, the exposure with response prevention was stopped and the medication was tapered off. Patients still continued to see their therapist or pharmacotherapist for supportive/evaluative meetings, lasting up to 20 minutes each, at regular intervals. Those who relapsed were removed from the study and offered open treatment.

Of the 87 patients who completed phase 1 of the initial trial, 48 were responders and were eligible to enter the discontinuation phase of the study. All but 2 of the responders actually participated in the discontinuation phase. Nine of the participants relapsed during the discontinuation phase.

Although the sample size was small in the 12-week discontinuation phase, and there was no randomization or control group, the following trends were highly suggestive. Responders who originally received either CBT alone or in combination with clomipramine had less severe OCD symptoms at the beginning of the discontinuation phase, were less likely to relapse during the discontinuation phase compared to patients who had received medication alone, and, if they did relapse, had a longer time to relapse following treatment discontinuation. This study suggests that combined treatment may have an important advantage in mitigating adverse effects of medication discontinuation.

Special Populations

One third to one half of adults with OCD develop the disorder during childhood or adolescence. The Pediatric OCD Treatment Study (POTS) Team published the first RCT exploring treatment efficacy of combined treatment in child and adolescent OCD patients (March et al., 2004). The multicenter study included 112 patients, aged 7 through 17, who were randomized to CBT, sertraline, combined treatment, or pill placebo groups for 12 weeks. Results showed that patients in the combined treatment group did better than either the CBT- or sertraline-alone groups, which did not differ from each other. Remission

rates were 54% in the combined group, 39% in the CBT-alone group, 21% in the sertraline-alone group, and 4% in the pill placebo group. The difference between the combined and CBT-alone groups did not reach statistical significance.

The POTS II study (Franklin et al., 2011) examined 124 patients aged 7 to 17 who had a partial response to an adequate SRI trial. Participants were randomized to three groups: (1) medication continuation only, (2) medication plus exposure and response prevention, and (3) medication plus "instruction in CBT," which involved pharmacotherapist delivery of truncated CBT sessions during the medication management sessions. The study found that augmentation with exposure and response prevention was effective, as was instruction in CBT; however, the gains made with instruction in CBT were minimal and not statistically significant. Reported response rates were 68.6% in the exposure and response prevention group, 34% in the instructions group, and 30% in the medication-alone group.

Storch and colleagues (2010) administered DCS in children and adolescents aged 8 to 17 who had been on stable medication doses at the time of study entry. Subjects underwent 10 60-minute CBT sessions and were given DCS at a dose of 0.7 mg/kg (based on a 50-mg dose for a 70-kg adult) or placebo 1 hour prior to the session. Although DCS appeared to improve outcomes, the difference from placebo failed to reach statistical significance.

Foa, Kozak, Steketee, and McCarthy (1992) sought to determine whether behavior therapy (exposure and response prevention) for the treatment of OCD was enhanced by prior treatment of comorbid depression. Patients ($N = 38$) were divided into highly depressed (BDI > 21) and mildly depressed (BDI < 20) groups, then randomly assigned to imipramine or pill placebo. Patients received medication for 6 weeks, which was continued while they began the behavior therapy sessions. These daily sessions were 2 hours each, lasting 3 weeks. Patients then had two home visits, each of 4 hours' duration. Participants then received 12 weekly, 45-minute supportive behavior therapy sessions. Medication was discontinued at 22 weeks. The results showed that imipramine did decrease depressive symptoms but did not seem to increase the likelihood of successful behavior therapy for OCD.

The consensus at present seems to advocate for either combined CBT with medication management or CBT alone for the treatment of OCD. There are data that suggest that combination therapy is somewhat better than CBT alone in children and adolescents, and likely in those who have failed to respond to the initial treatment approach. In a general adult sample, there is little evidence that the addition of pharmacotherapy is superior to CBT alone, but there is no evidence that combined treatment has any negative effects (e.g., no greater likelihood of relapse after discontinuation). More research is needed to determine whether there are individuals who would be better suited to psychotherapy alone, medication alone, or combined treatment.

POSTTRAUMATIC STRESS DISORDER

While there have been numerous studies showing the efficacy of both pharmacological and psychosocial therapies in the treatment of PTSD, the few studies examining the efficacy of the combination have been small and fraught with methodological limitations. However, expert recommendations and common practice often espouse the usefulness of this combination.

Otto and colleagues (2003) conducted one of the earliest of these small studies in 2003, comparing the combination of sertraline plus CBT to treatment with sertraline alone in 10 female Cambodian refugees. All subjects had previously failed to respond to treatment with an SSRI other than sertraline plus clonazepam. Although inclusion and exclusion criteria were not clear, it appears that the two groups had similar and significant psychiatric comorbidity. Enrolled subjects were continued on clonazepam and started on open-label dosing of sertraline. Group CBT was conducted with five of the study participants. The results of this pilot study suggest that the women in the CBT group improved more than the women in the sertraline-alone group, particularly on measures of misinterpretation of culturally relevant somatic stimuli.

Rothbaum and colleagues (2006) compared sertraline alone and sertraline combined with prolonged exposure therapy in sertraline responders in a two-phase study where 88 subjects entered a 10-week, open-label sertraline trial and were required to demonstrate at least 20% improvement in PTSD severity to move on to phase 2. The 65 subjects who met this criterion were randomized to either 5

weeks of continued sertraline alone or sertraline with prolonged exposure therapy. Those randomized to the sertraline-only group demonstrated no further improvement. Sertraline plus exposure did result in some further reduction in symptom severity, but the results failed to reach statistical significance. In a secondary analysis, the authors examined two different groups, which they labeled as partial medication responders and excellent medication responders. In this analysis, they found that the partial medication responders derived more substantial benefit from exposure therapy than did the excellent medication responders.

Simon and colleagues (2008) compared prolonged exposure therapy alone or in combination with paroxetine in a two-phase trial. A total of 68 participants entered the first phase of this study, in which all received eight 90- to 120-minute exposure sessions. Those still symptomatic after seven sessions were randomized to paroxetine or placebo along with five addition exposure sessions. Of the 68 subjects who entered the trial, 25 were eligible for randomization to paroxetine or placebo, and 23 went on to enter the second phase of the study. The addition of paroxetine did not confer any benefit over exposure alone in this study.

Schneier and colleagues (2012) also studied 37 participants who were randomly assigned to 10 weeks of prolonged exposure therapy with either paroxetine or placebo in survivors of the September 11 attacks. There was a 12-week continuation phase of paroxetine or placebo but no exposure therapy. For the duration of the combined treatment phase, paroxetine plus exposure was superior to placebo plus exposure, with a number needed to treat of 3 (i.e., three patients needed to be treated with combined treatment in order to realize one remission that would not have also occurred with placebo plus exposure), although the placebo group also had clinically meaningful improvements. Unlike the initial combined therapy phase, results of the 12-week continuation phase did not demonstrate a significant between-group difference. The authors suggest that the study does show a benefit of addition of paroxetine, with the remission rate in the paroxetine group being double that of the placebo group. They postulate that if the study had been adequately powered, a significant difference would have been uncovered. They point out that this study differs from Simon and colleagues' study in that all subjects were randomized to paroxetine or placebo, rather than purely a sample with an inadequate response to exposure therapy alone.

Only one study has examined combined medication and psychotherapy in adolescents. Cohen and colleagues (2007) studied trauma-focused CBT alone or combined with sertraline in subjects aged 10 to 17 who had experienced sexual abuse. The initial study design planned to include 40 participants in each group; however, there was significant difficulty in recruitment, which the authors attribute to the black box warning placed on SSRIs in 2004. Ultimately, 22 participants were randomly assigned to each treatment group. The study did not demonstrate a benefit of combining CBT with sertraline instead of with placebo.

Although expert opinion continues to encourage the combination of medication and psychotherapy for the treatment of PTSD, there is little evidence to support this recommendation. In fact, in 2010, a Cochrane report (Hetrick, Purcell, Garner, & Parslow, 2010) including four studies (Cohen et al., 2007; Otto et al., 2003; Rothbaum et al., 2006; Simon et al., 2008) concluded that there is not enough evidence to support or refute the combination of psychotherapy and medication in the treatment of PTSD.

Another approach that has been used in the treatment of PTSD is the addition of medications administered at the time of psychotherapy to enhance its effectiveness. Three studies have combined psychotherapy with DCS. De Kleine and colleagues (2012) administered 50 mg of DCS or placebo 1 hour prior to exposure sessions in 67 subjects and failed to find a difference in outcome between the two groups. However, the study did allow early completers; if both the subject and the therapist felt the patient was better, he or she did not have to finish all planned psychotherapy sessions. A secondary analysis revealed that DCS did enhance outcomes in the group that completed all therapy sessions, leading to the conclusion that DCS may be helpful in those who do not have as robust a response to psychotherapy. The study had a high dropout rate ($n = 22$); 45 participants completed the study, and 8 who dropped out prior to receiving any exposure session were not included in the final analysis.

Litz and colleagues (2012) studied DCS in 26 Iraq and Afghanistan veterans with combat-related PTSD who underwent six 60- to 90-minute exposure therapy sessions. They were given 50 mg DCS or placebo prior to sessions 2 through 5, which involved

imaginal exposure. Participants could continue non–exposure-based psychotherapy as well as psychotropic medications as long as the dose was stable for 2 months prior to study entry. The DCS group had a poorer outcome than the placebo group; the authors speculate that DCS might have inadvertently reconsolidated frightening memories evoked by the therapy itself. They also point out that the sample size was small, making it difficult to draw firm conclusions.

In sum, study results involving DCS have been disappointing. Methodological difficulties including sample size and lack of clarity regarding the timing of DCS dosing may have contributed to the results. There is currently no evidence that DCS enhances outcomes in PTSD patients, but further research in this area with larger and more robust studies could lead to alternative conclusions.

Another intervention, 3,4-methylenedioxy-N-methylamphetamine (MDMA), was classified as a Schedule I drug in 1985, but prior to this there were case reports of it augmenting psychotherapy, decreasing fear, and enhancing alertness. Mithoefer and colleagues (2011) randomized 20 subjects to MDMA or placebo to enhance psychotherapy. Participants in this study were required to have treatment-resistant PTSD (failed to respond to 3 months of SSRI or SNRI treatment plus 6 months of psychotherapy). The study was also limited to individuals with crime- or war-related trauma. All participants were tapered off psychotropic medications prior to study entry, with the exception of sedatives and hypnotics taken on an as-needed basis for anxiety or insomnia.

Subjects underwent two 8-hour psychotherapy sessions with MDMA or placebo 3 to 5 weeks apart. These sessions followed a manualized psychotherapy developed specifically for this study. Patients were also offered weekly standard psychotherapy sessions in between MDMA-assisted sessions. A 125-mg dose of MDMA was administered at the beginning of psychotherapy followed by an optional supplemental 62.5-mg dose given 2 to 2.5 hours later. The session lasted the entire day, and the subjects remained overnight. Zolpidem was available for insomnia.

Following the two sessions, the blind was broken, and the placebo group was offered a crossover. Seven of the eight subjects initially randomized to placebo chose to go on to the crossover phase. Ten out of 12 participants initially randomized to MDMA no longer met criteria for PTSD at the end of the study compared with 2 out of 8 in the placebo group. In the crossover phase, all seven subjects had a response to MDMA-assisted psychotherapy. In addition to the small sample size, the authors point out that there was difficulty with blinding in this study and that most of the participants correctly guessed their treatment assignment.

Mithoefer and colleagues (2013) followed up (17 to 74 months, with an average of follow-up time of 3.5 years) on 19 of the subjects in the initial study. Sixteen of the 19 completed the follow-up phase. The improvements were durable; only two subjects relapsed in this group. No neurocognitive decline or new-onset substance abuse was observed, as had been feared with the use of this Schedule I drug. As this was a naturalistic study, the authors make the argument that all the subjects had treatment-refractory PTSD upon entering the study and were unlikely to have achieved sustained remission from interventions during the follow-up period.

Oehen, Traber, Widmer, and Schnyder (2013) enrolled 12 participants with treatment-resistant PTSD in a study that compared full-dose versus low-dose MDMA, which was administered as an active placebo to enhance the study blind. Participants underwent three MDMA-assisted, day-long psychotherapy sessions with overnight stay, similar to the psychotherapy design of Mithoefer and colleagues' study. Participants were defined as treatment-resistant if they had failed to respond to 6 months of psychotherapy or 3 months of SSRI. All psychotropic medications (other than gabapentin used for pain control) were tapered. Existing psychotherapy could be continued as long as no changes were made.

Eleven subjects completed the study. Eight were randomized to full-dose MDMA, 125 mg at the start of psychotherapy plus 62.5 mg 2.5 hours later. Four were randomized to active placebo consisting of low-dose (25-mg) MDMA at the start of psychotherapy and 12.5 mg given 2.5 hours later. After the three initial sessions were complete, the active placebo group was given full-dose MDMA in a crossover phase. After an initial analysis, two more psychotherapy sessions were added because many were judged to have had an insufficient response. At the end of the study, four of the participants in the MDMA group were improved but still met criteria for PTSD, while no patients in the placebo group responded. The between-group difference did not reach statistical significance. Even with the use of an active placebo, many participants and investigators accurately guessed randomization.

Both studies involving MDMA-assisted psychotherapy were very small and considered to be pilot studies. The results suggest some promise of using MDMA in certain PTSD patients, but risks that may be associated with longer-term use of this drug with a potential for abuse will have to be carefully considered. Similar to results in OCD, there is yet insufficient evidence to support or refute combined medication and psychotherapy for PTSD.

GENERALIZED ANXIETY DISORDER

In the years since the previous edition of this text, there have been few new RCTs comparing combined treatment with monotherapy in GAD. Benzodiazepines have been commonly prescribed for anxiety, but few studies were conducted to test their effectiveness in combination with a psychosocial treatment such as CBT. Powers and colleagues (1990) compared diazepam alone, placebo alone, CBT alone, diazepam plus CBT, and placebo plus CBT for 8 weeks in 113 subjects (double-blind). The dose of diazepam in any treatment group was 5 mg taken three times daily. Outcome measures were the Hamilton Rating Scale for Anxiety (HRSA), General Health Questionnaire (GHQ), and a self-report measure of change. Although the results demonstrated that CBT plus diazepam and CBT plus placebo as well as CBT alone were effective, and there were no differences among the CBT groups, the study did not use a structured interview for diagnosis, and diagnostic criteria was based on *DSM-III*, which limits its comparison to newer studies.

Buspirone was tested on 60 patients with GAD (Bond, Wingrove, Curran, & Lader, 2002) randomized to one of four treatment conditions: buspirone and anxiety management training, buspirone and nondirective therapy, placebo and anxiety management training, and placebo and nondirective therapy, for 8 weeks.

Nondirective therapy involved the patients talking freely with the therapist, acknowledging and reflecting back feelings discussed, using open-ended questions in a nonjudgmental manner. Anxiety management training incorporated some elements of CBT: psychoeducation, progressive muscle relaxation, and homework assignments. In addition, avoidance behaviors and anxiety triggers were explored, as well as the relationship among thoughts, feelings, and symptoms. Negative thoughts were recorded and challenged, possibly in a similar manner to cognitive therapy, but no further elaboration of the technique was presented. Both types of psychotherapy continued weekly, consisting of 45-minute sessions for 7 weeks.

The medication and placebo used flexible dosing, beginning at 5 mg in three daily capsules increased to six capsules if necessary for 8 weeks. Whether the clinicians and patients were blind to placebo versus buspirone was not mentioned. Outcome was measured using the HRSA, administered by a blind evaluator. Self-reports included the Hospital Anxiety and Depression Scale, the Zung Self Rating Anxiety Scale, the GHQ, the Cognitive Checklist, and the Mood Rating Scale.

Results showed that in 44 of 60 participants who completed the trial, there was no significant difference in outcome among the groups; all showed a 50% reduction on HRSA, indicating some improvement. When comparing the completer analysis to the intent-to-treat analysis, similar results occurred.

This study makes the case that psychotherapy is helpful in the treatment of GAD with or without the addition of buspirone. It is difficult to compare the results of this research to other studies of GAD using CBT, since only improvement on HRSA and self-reports were measured. Most other studies institute remission or response criteria and measure rate of response. Many clinicians also agree that dosages of 30 mg or less per day of buspirone, such as used in this study, are grossly subtherapeutic.

The duration of treatment in this trial was rather short (only 8 weeks), whereas other studies using CBT have been conducted for a minimum of 12 weeks (Borkovec, Newman, Pincus, & Lytle, 2002). The major hallmark of GAD is uncontrollable worry. The HRSA measures worry but not exclusively; rather, the items combine anxious mood, worry, fearful anticipation, and irritability. Other instruments have been used that focus primarily on worry (e.g., Penn State Worry Questionnaire [PSWQ]; Meyer, Miller, Metzger, & Borkovec, 1990) and make comparisons between studies easier.

Antidepressants have also been used to treat GAD. Crits-Christoph and colleagues (2011) tested the effectiveness of combining venlafaxine extended-release with CBT in a primary care sample of patients with GAD. This sample consisted of 77 patients randomly chosen from a total of 334 who had enrolled in a medication-only trial of venlafaxine extended-release.

What is unique in this sample is that participants were invited to enroll rather than being treatment-seeking for CBT. From the 77 invited, only 29 agreed to participate, while only 26 attended at least one session. Outcome measures included HRSA, GHQ, PSWQ. CBT treatment lasted for 12 sessions.

The outcome measures compared the CBT-plus-venlafaxine-extended-release group (randomly offered this treatment) to those patients who received venlafaxine extended-release alone (never offered CBT). Based on HRSA measures, there was no significant difference between the two groups (intent-to-treat), nor were there any significant differences on any other outcome measures. In this study sample of primary care patients who were medication-seeking, adding CBT to medication (venlafaxine extended-release) did not significantly improve the outcome. It should be noted that patients in this sample were excluded if they had comorbid major depression or any episode of MDD in the past 6 months. In addition, CBT lasted only 12 sessions. Other CBT treatment studies for GAD have extended the duration to 16 sessions to increase the likelihood of treatment response.

GAD is common among older adults, and pathological worry in this group may be more difficult to treat. Wetherell and colleagues (2013) recruited 73 adults over age 60 with GAD from three clinics (Pittsburgh, St. Louis, San Diego), all receiving 12 weeks of open-label escitalopram, and randomly assigned them to one of four conditions: 16 weeks of escitalopram plus modular CBT followed by maintenance escitalopram for 28 weeks, escitalopram alone followed by maintenance citalopram, escitalopram plus CBT followed by pill placebo, and escitalopram alone followed by pill placebo. Measures included HRSA and PSWQ. Depressive comorbidity was not excluded, but psychosis, suicidality, and severe cognitive impairment were exclusion criteria.

Modular CBT was a 16-week, manualized protocol targeting worry and anxiety. Modules included psychoeducation, self-monitoring, relaxation exercises, cognitive restructuring, and problem solving. In addition, family members were invited to attend one session and were taught about GAD. Those participants who were depressed (score of 3 or 4 on HAM-A depression item for two consecutive assessments) were also administered a behavioral activation module. For participants who had a comorbid anxiety disorder, an exposure module was administered. Participants with insomnia (score of 3 or 4 on HAM-A sleep item for two consecutive assessments) received a sleep hygiene module.

Participants began with escitalopram treatment, then entered the augmentation phase, where those in the CBT group received 16 sessions. During the maintenance phase, those on escitalopram who were to receive pill placebo were tapered off and started on placebo while the continuation group stayed on the same dose. Those participants who received CBT were eligible for up to three booster sessions of CBT during the maintenance phase.

Relapse in this trial was based on two consecutive assessments and defined as an HAM-A score 14 or higher or at least 5 points greater than the lowest score rated during the augmentation phase, and meeting *DSM-IV* criteria for GAD (without duration criterion). Automatically meeting the criteria for MDD was also considered relapse regardless of the HAM-A score.

Results were favorable for the patients receiving escitalopram plus CBT augmentation; they showed lower PSWQ scores (improvement in pathological worry) than the escitalopram-only group. HAM-A scores were not significantly different between groups, but when the authors analyzed only those whose score was greater than 14 at the time of augmentation, results showed a preference in the CBT group, since 52.6% were considered responders while only 26.7% of the other group achieved response.

The results of maintenance treatment demonstrated greater relapse in the placebo group (46%) than the escitalopram group (2.7). Because the effect of maintenance escitalopram was so large, the authors analyzed the placebo group to determine the effects of CBT on relapse and found a significant difference. Those participants on placebo who received CBT augmentation relapsed less often (only 25%) compared to the placebo-only group (66.4%). There was no significant difference in relapse rates between the escitalopram-only group and the CBT-plus-placebo group.

In summary, maintenance SSRI medication augmented with CBT in this older adult population was not only effective in reducing worry but also protective of relapse. From these data, we can conclude that adding CBT to an SSRI is an effective treatment option.

Although GAD is frequently comorbid with MDD (62% of individuals with GAD have had a history of MDD; Wittchen et al., 1994), there are almost

no RCTs combining psychotherapy with medication for this comorbid group. One study (Aaronson, Terranova, Pievsky & Hirschowitz, unpublished manuscript), randomly treated 62 adults with GAD and MDD, aged 18 to 65, with either CBT plus quetiapine extended-release or CBT plus placebo. Participants had to meet full criteria for both disorders on a structured interview (Mini International Neuropsychiatric Interview [MINI]) and in a psychiatric evaluation and had no history of bipolar disorder, any psychotic disorder or psychosis, eating disorder, or current substance use disorder. Any unstable medical condition in which taking quetiapine was contraindicated was also an exclusion criterion.

Treatment lasted 16 weeks (although 16 sessions of CBT may have taken more than 16 weeks to complete) and patients were seen weekly. Depression symptoms were measured by the MADRS weekly and anxiety was measured using the HRSA. CGI for improvement and severity were also measured weekly. Worry and mood were also measured by self-report at baseline and at 4, 8, 12 and 16 weeks.

CBT included psychoeducation about anxiety and depression, deep breathing, progressive muscle relaxation exercise, cognitive restructuring of rumination and worry, behavioral activation for amotivation in depression, situational exposure for phobic avoidance, and affect exposure (emotions that are typically avoided through worry). Quetiapine extended-release dosing started at 50 mg per week with a target of 150 mg by week 3. If patients did not tolerate the increase in dose, they were decreased to the lower dose, with a minimum of 50 mg throughout the study. Study researchers tried to make the dose as flexible as possible both to accommodate patients and to reflect clinical practice, yet keep the necessary rigor of a clinical trial.

Of the 62 participants randomized, 7 dropped out before beginning any treatment. The attrition rate in this trial was high—17 dropped out or were exited—due to fears about taking an antipsychotic medication and its side effects, or time commitment (no evening appointments). Response was measured by at least a 50% decrease in both MADRS and HRSA from baseline and a CGI score of 1 or 2 (for both improvement and severity).

When the total sample was included, there was no significant difference in response between the two treatment groups, although there was significant improvement in all participants. In the completer sample, there was a significant difference in outcome. In the combined group, 81% responded while 47% of the CBT-plus-placebo group responded.

The small sample size is a major limitation, but this suggests a potentially effective treatment for a subgroup of patients who typically do not have good outcomes in usual treatment.

Clearly, more research is needed for efficacy testing of combined treatment of GAD, especially involving SSRIs as well as other novel pharmacotherapies and a full course of CBT that includes cognitive restructuring, worry reduction, exposure (to emotions, thoughts, and situations), mindfulness, and progressive muscle relaxation techniques.

Generalized Anxiety Disorder and Social Anxiety Disorder in Children

The Child-Adolescent Anxiety Multimodal Study (CAMS) was a multicenter, two-phase RCT for children and adolescents aged 7 to 17 with separation anxiety disorder, GAD, or SAD. Phase I, which lasted 12 weeks, recruited children from six sites and compared CBT, sertraline, CBT plus sertraline, and placebo (Walkup et al., 2008). Phase II lasted 6 months, extending treatment for those who responded in phase I.

Inclusion criteria were meeting full *DSM-IV-TR* criteria for GAD, SAD, or separation anxiety disorder with impairment and an IQ of at least 80. Additional diagnoses of ADHD, OCD, PTSD, oppositional defiant disorder, and conduct disorder were allowed if less severe than the target disorders. Exclusion criteria included significant school refusal due to anxiety, unstable medical conditions, and failed response to two adequate trials of SSRI or CBT treatment. Current substance use disorder and major depression requiring medication treatment were also exclusionary.

Of the 524 eligible subjects, 488 were randomized and 57 stopped treatment (11.7%), with participants in the CBT group less likely to drop out. There were 140 children in the combination group, 133 in the sertraline group, 139 in the CBT group, and 76 in the placebo group.

The CBT treatment was conducted weekly for 14 sessions lasting 60 minutes (two of those sessions were parent-only sessions). The interventions used the Coping CAT manual and included anxiety management skills and exposure. The sertraline or placebo

was administered in a fixed-flexible schedule, with a starting dose of 25 mg adjusted to a maximum of 200 mg by week 8; sessions occurred weekly for 30 to 60 minutes, where anxiety was rated and side effects were discussed. The combination therapy group whenever possible met on the same day for CBT and medication visits.

Outcome measures were CGI-I, Pediatric Anxiety Rating Scale, and Children's Global Assessment Scale administered at 4, 8, and 12 weeks, and response was defined as a 1 or 2 on the CGI. In this study, the combined treatment group demonstrated the greatest response, 80.7%, significantly better than the monotherapies. While the other groups demonstrated significant improvement over placebo, the CBT group had a response of 59.7%, sertraline 54.9%, and placebo, 23.7%; the two monotherapies were equally as effective. The sertraline group did not experience any more suicidal or homicidal ideation than the placebo group but experienced more insomnia, fatigue, sedation, and restlessness than the CBT group.

Phase II of the CAMS study involved 6 months of maintenance treatment followed by a 24-week and a 36-week assessment (Piacentini et al., 2014). Maintenance CBT involved monthly sessions where no new material was added, but new or worsening symptoms were addressed using techniques learned in acute treatment. Medication maintenance visits were also monthly, with the dosage remaining constant unless side effects emerged, in which case the dosage was decreased. Again, the combined treatment group continued in the same manner as the monotherapy groups, meeting monthly for both medical visits and CBT booster sessions on the same day.

The same response criteria held for phase II: a CGI-I of 1 or 2. In addition, an excellent treatment response category was defined as a CGI-I of 1. Remission was defined as a CGI-S as 1 or 2 or no longer meeting Anxiety Diagnostic Interview Schedule, child version criteria.

Of the 370 participants who completed acute treatment, 322 (78.2%) completed the assessment at week 24 and 325 (78.9%) completed the week 36 assessment. The combined group remained about the same from 12 weeks to 24 and 36 weeks (81% to 82% responders), while the sertraline and CBT groups continued to improve in outcome so that at 36 weeks, there was no statistically significant difference among the groups. When considering excellent response, combined treatment was significantly better than CBT at 12 weeks, it just missed significance at 24 weeks ($p = 0.055$), and it was not significant at 36 weeks. Using remission status based on diagnosis, there was a significant difference; the combined group experienced greater remission than either monotherapy, and the monotherapies did not differ from each other. Using the CGI-S remission criteria, there was a trend toward significance for the combined group ($p = 0.01$), but that disappeared at 36 weeks.

In summary, for socially anxious, generally anxious, and separation anxious children and adolescents, the combination of sertraline and CBT was most efficacious at the 12-week acute treatment point, but with continued maintenance treatment, the monotherapies caught up at 24 and 36 weeks.

SOCIAL ANXIETY DISORDER

There is a paucity of RCTs for SAD comparing medication, psychotherapy, and their combination, whereas the number of such trials for monotherapy comparisons abound. Of the four RCTs that were conducted since 1990, three were conducted in an academic psychiatric setting employing trained clinicians; the other was conducted in a primary care setting with medical practitioners.

One early study by Clark and Agras (1991) compared the effectiveness of buspirone alone, placebo alone, CBT plus buspirone, and CBT plus placebo for 6 weeks in 34 musicians with performance anxiety, aged 18 to 60. The CBT was delivered in a group format of five or six participants and included cognitive restructuring, coping models, and exposure. Buspirone was administered in 5-mg doses, three times per day, and increased as needed up to 12 pills per day. Outcome was measured through subjective anxiety ratings and heart rate during laboratory performance. Results showed significantly greater improvement in the CBT-plus-placebo group over not only the buspirone-only or placebo-only groups, but also the CBT-plus-buspirone group. Buspirone was not effective at all in performance anxiety in musicians.

Davidson and colleagues (2004) conducted a large RCT for generalized SAD using fluoxetine, CBT, their combination, and placebo at two sites, randomizing 295 adults to 14 weeks of treatment in one of five groups: fluoxetine alone ($n = 57$), comprehensive group CBT alone ($n = 60$), fluoxetine and comprehensive group CBT combined ($n = 59$), placebo

plus comprehensive group CBT (n = 59), and placebo alone (n = 60). Exclusion criteria were similar to those for other RCTs for anxiety disorders: schizophrenia, bipolar disorder, current substance use disorder, cognitive impairment or organic brain syndrome, any unstable medical condition, MDD within the past 6 months, and another primary anxiety disorder.

Fluoxetine treatment and placebo, both administered double-blind by a psychiatrist following a manual, were initiated at 10 mg and increased to 20 mg on day 8, to 30 mg on day 15, and to 40 mg on day 29 (the target dose). If patients failed to achieve response at 40 mg, the dose was raised to 50 mg on day 43 and to 60 mg on day 57. Patients were seen weekly for 4 weeks, then every other week for the rest of the 10 weeks. The comprehensive group CBT involved psychoeducation, social skills training, cognitive restructuring, and in vivo exposure during the 14 weekly sessions. This type of CBT differs in the addition of social skills training and two sessions in which the patients were taught how to begin a conversation with a stranger and how to make eye contact. Group sessions were led by two extensively trained therapists and comprised five or six patients; the length of group sessions was not discussed.

Outcome was measured using the Brief Social Phobia Scale and the CGI, both rated by an independent evaluator. A videotaped role-play test of social skills was conducted before and after treatment and served as a secondary outcome measure. Of the 295 randomized patients, 211 (72%) completed the 14 weeks of treatment, with 5% (n = 16) dropping out before treatment began. In pairwise comparisons, the placebo-only group experienced more dropouts than the group receiving comprehensive group CBT only and the group receiving comprehensive group CBT plus placebo.

Based on CGI scores as the response criterion, the intent-to-treat response rates were 50.9% for fluoxetine alone, 51.7% for comprehensive group CBT alone, 54.2% for combined fluoxetine and comprehensive group CBT, 50.8% for comprehensive group CBT plus placebo, and 31.7% for placebo only, demonstrating only a trend for significance (p = 0.09). When pairwise comparisons were tested, all treatments were significantly more effective than placebo, with combined treatment demonstrating slightly greater statistical significance (p = 0.01; p = 0.03 for all other comparisons). The completer response rates were higher: fluoxetine 64.1%, comprehensive group CBT 64.6%, combined treatment 66.7%, comprehensive group CBT plus placebo 59.6%, and placebo 40.5%. Again, overall, there was a trend toward significance (p = 0.09), but the pairwise comparisons demonstrated that active treatment was more effective than placebo except for the patients receiving comprehensive group CBT plus placebo; this group only showed a trend toward significance (p = 0.08). The combined treatment group demonstrated the greatest statistical significance (p = 0.01), with comprehensive group CBT next (p = 0.02), and fluoxetine alone last (p = 0.03).

The two phobia measures demonstrated a significant difference in outcome between the active treatments and placebo, but in pairwise comparisons, fluoxetine alone followed by comprehensive group CBT alone demonstrated the fastest onset of action. In this very-well-conducted RCT, there was no significant benefit to combined CBT and medication for SAD.

The second RCT for SAD was conducted by Clark and colleagues (2003) in England. Patients aged 18 to 60 with generalized SAD of at least 6 months' duration without current MDD, bipolar disorder, psychosis, or substance use disorder were included. No participants were accepted if they had previous treatment experience with cognitive or exposure therapy or an SSRI.

The 60 SAD patients were evenly randomized to one of three treatment conditions: cognitive therapy alone, fluoxetine plus self-exposure, and placebo plus self-exposure. Acute treatment lasted for 16 weeks, followed by a 3-month maintenance period. All patients were assessed at 12 months for follow-up.

The cognitive treatment, based on the model of Clark and Wells, focused on the ways that social phobia is maintained through thoughts and safety behaviors. One of the treatment components involved helping patients change their self-focus (constant monitoring of their own sensations and worry about how others perceive them) to an external one (e.g., the social situation in which they are engaged). The treatment also incorporated videotape feedback to correct distorted self-images frequently held by socially phobic patients. In addition to receiving exposure therapy, patients were prepared in advance for what they feared would occur and then were tested for whether the feared event actually occurred. Cognitive restructuring was implemented to change dysfunctional assumptions.

Pharmacotherapists were psychiatrists with experience using SSRIs but with little formal CBT training. The fluoxetine or placebo treatment groups received 20-mg capsules, with the first dosage increase to 40 mg at week 2 or 3, increasing to a maximum of 60 mg if needed. Patients were told that fluoxetine would make them more confident in social situations by correcting a neurochemical disturbance and were advised to systematically expose themselves to social situations to derive maximum benefit from the medication.

Measures of social anxiety in this study were the Social Phobia Scale, the Social Interaction Anxiety Scale, the Liebowitz Social Anxiety Scale (LSAS), the Fear Questionnaire Social Phobia subscale, the Fear of Negative Evaluation Scale, and the Social Phobia Weekly Summary Scale (a self-report of social anxiety, social avoidance, self-focused vs. external attention, anticipatory processing, and post-event rumination). The Beck Anxiety Index and the BDI were used to assess mood.

The sample was 52% female; 43% met criteria for avoidant personality disorder. There were no significant differences between the treatment groups on demographic variables. Six patients did not complete the treatment phase. Of the 54 completers, 20 received cognitive therapy, 17 received fluoxetine plus exposure, and 17 received placebo plus exposure.

At the end of the 16-week treatment phase, cognitive therapy was significantly more effective on a composite measure of social anxiety than either combined treatment or placebo. Fluoxetine plus exposure was not significantly different than placebo plus exposure on this composite measure. All three treatment groups demonstrated a significant decrease in all measures, composite and individual, from baseline to posttreatment. All three treatment groups demonstrated significant improvement in mood measures from baseline to posttreatment, but there was no difference among the groups. These results are based on an intent-to-treat analysis.

Patients in the cognitive-therapy-only group and the fluoxetine-plus-exposure group were entered into the maintenance phase after the acute-treatment phase. The placebo-plus-exposure patients were withdrawn from the study. During the maintenance treatment, cognitive therapy patients received three monthly booster sessions. The fluoxetine-plus-exposure patients continued for 3 months on their full dose, which was then gradually tapered over 3 to 6 weeks. Measurements were again taken, and the results showed that the cognitive therapy patients maintained their treatment gains, and the fluoxetine-plus-exposure patients continued to improve. The cognitive therapy group continued to demonstrate significantly better outcome after the maintenance phase. These differences were also found at the 12-month follow-up: Cognitive therapy was superior to fluoxetine plus exposure on both composite and individual social anxiety measures.

The study authors also calculated effect sizes at posttreatment for the treatment groups: 2.14 for the cognitive therapy group, 0.92 for the fluoxetine group, and 0.56 for the placebo group. The maintenance phase effect size was 2.57 for the cognitive therapy group and 1.14 for the fluoxetine group. The 12-month follow-up effect size was 2.53 for the cognitive therapy group and 1.36 for the fluoxetine group.

In this trial, combined treatment was not better than monotherapy (cognitive therapy) in the treatment of generalized SAD, although significant improvement was demonstrated. Cognitive therapy was substantially more effective than self-directed exposure with or without fluoxetine.

The most recent study combining medication and CBT for generalized SAD was conducted by Blanco and colleagues (2010), who followed up on previous work using phenelzine alone and in combination with group CBT. The two-site study (conducted in New York and Philadelphia) randomized 166 adults aged 18 to 65 with SAD without a history of schizophrenia, bipolar disorder, current MDD or substance use disorder, previous treatment failure with phenelzine, and/or six or more CBT sessions. One hundred twenty-eight patients (New York, $n = 84$; Philadelphia, $n = 44$) were randomly assigned to one of four conditions: phenelzine alone ($n = 35$); group CBT alone ($n = 34$); combined phenelzine plus group CBT ($n = 32$); or pill placebo alone ($n = 27$). This four-phase trial included a 12-week acute-treatment phase, a 12-week intensive continuation phase, a 28-week maintenance phase, and a 12-month naturalistic follow-up phase.

The group CBT was conducted with four to six participants meeting weekly in 2.5-hour sessions led by two therapists for 12 weeks. Treatment included cognitive restructuring (awareness of relationship between anxiety and automatic thoughts and the rational alternatives) and role-playing of exposure to feared situations, followed by in vivo exposures. The

pharmacotherapy began with 15 mg of phenelzine or placebo per day for 3 days increased to 30 mg/day for 4 days, to 45 mg/day for week 2, up to 60 mg/day for weeks 3 and 4. If necessary for clinical progress, doses up to 75 mg/day for week 5 and as high as 90 mg/day for weeks 6 to 12 were permitted. All medication participants were told to expose themselves to feared situations, and that the medication would make that easier, but no specific instructions for practicing exposure were given. The patients receiving phenelzine and group CBT began medication and therapy at the same time. Both clinicians in that group were blind as to any other treatment, nor could clinicians discuss treatment with each other.

Measures for outcome included LSAS, CGI modified for SAD and HRSD as well as self-reports (FQ, Social Phobia Scale, Social Interaction Anxiety Scale, and Sheehan Disability Scale) collected at baseline and at weeks 6, 12, and 24. Response was defined as CGI score of 1 or 2 at week 12, while remission was defined as CGI score of 1 or 2 plus LSAS score of 30 or less.

There were no significant differences between groups at baseline except for the combined treatment group, which demonstrated less severity of SAD on several measures. Although there were some site differences in the demographic variables, these did not affect treatment outcome. There were also no significant differences among groups in the number of withdrawn subjects or for any demographic variables between those who continued and those who withdrew.

All primary and secondary outcome results demonstrated significant improvement in the phenelzine group and the combined group compared to placebo. The group CBT group was not significantly different from placebo. The odds ratio demonstrated that the combined group was 5.1 times more likely to improve compared to placebo, while the other three groups did not demonstrate significant odds of improving.

In the combined group 46.9% achieved remission based on CGI, while 22.1% of the phenelzine group, 8.8% of the group CBT group, and 7.4% of the placebo group remitted (the latter three groups were not significantly different from each other). Using the LSAS as outcome, the remission rates were as follows: combined group 59.4%; phenelzine 20%; group CBT 20.6%; and placebo 11.1%. The combined group was significantly better then the monotherapies which were not better than placebo or from each other. In this study, acute combined treatment was superior, followed by phenelzine alone, then group CBT, and then placebo. These same remission and response rates remained after the 12-week continuation phase.

The primary care RCT for SAD was conducted by Blomhoff and colleagues (2001) in Norway and Sweden. They randomly treated 387 socially anxious patients with sertraline or placebo. Half of those patients were randomly assigned to exposure therapy or general medical care. There were 98 patients in the sertraline-plus-exposure-therapy group, 98 in the placebo-plus-exposure-therapy group, 96 in the sertraline-plus-general-care group, and 95 in the placebo-plus-general-care group. All treatment was provided by medical practitioners who received training in diagnostic interviewing and exposure therapy.

One hundred thirty-five subjects from the sample had a comorbid diagnosis, but only 2% had comorbid dysthymia. Excluded diagnoses were history of bipolar disorder, psychosis, or panic disorder that began before social phobia, as well as current MDD, any other anxiety disorder, eating disorder, or substance use disorder.

Measures used to determine outcome were the SPS, the Clinical Global Impression-Social Phobia Scale (CGI-SP), and the MADRS. Diagnosis was assessed using the MINI. Clinicians in this study included 50 physicians who underwent a 30-hour training program to conduct the MINI and other rating scales, to make a reliable diagnosis of social phobia, and to conduct the exposure therapy component of the treatment. Training involved lectures, videotapes, manuals, and group supervision.

The sertraline treatment or placebo began with one pill daily (50-mg dose) for 4 weeks, and then the dosage was increased to 100 mg daily (two pills). At weeks 8 and 12, the dosage was again increased to a maximum of 150 mg if needed. The 12-week dosage was maintained through week 16 if tolerated. Patients were seen for nine visits over the 16 weeks of the study. Pharmacotherapy adherence was evaluated regularly through blood levels, as well as through pill counts.

The general medical care component of the study was based on NIMH guidelines for clinical management of mood disorders: general therapeutic support, reassurance and encouragement with some advice, and allowing the patient to express fears and concerns. No interpretations of patient behavior or specific behavioral instructions were allowed.

The exposure therapy component, conducted during eight 15- to 20-minute sessions over the first 12 weeks of the study, consisted of psychoeducation, with explanations of the treatment and the identified problems, and homework assignments and instructions for the patient to gradually expose himself or herself to feared situations outside the session meeting, using rating scales to measure the level of anxiety. The goal was for the patient to slowly decrease his or her anxiety as each exposure occurred. The physician's role throughout the 12 weeks of exposure therapy was to identify goals, to explore new coping strategies, and to support self-exposure.

Outcome was measured on three levels (responder, partial responder, and nonresponder) based on the CGI-SP and the SPS (self-report). Ratings were made at weeks 4, 8, 12, 16, and 24. Response criteria were a 50% reduction on SPS from baseline, a CGI-SP severity rating of 1 or 2, and a CGI-SP improvement rating of 1 or 2. Nonresponse criteria were less than a 25% reduction on SPS from baseline and a CGI-SP improvement rating of no change or worse (4 or higher). Partial response criteria were scores between response and nonresponse.

The protocol called for treatment withdrawal after 16 weeks if nonresponse occurred, and 44 (11%) patients were withdrawn. The intent-to-treat group consisted of 354 patients. There was a significant difference in response between those patients receiving sertraline and those receiving placebo, but only a trend toward significance between patients in the exposure group compared with the general care group ($p = 0.08$). The combined sertraline and exposure group had an intent-to-treat response rate of 40.8% ($n = 40$) and a completer response rate of 45.5%. The sertraline-only group had an intent-to-treat response rate of 36.4% and a completer response rate of 40.2%. The intent-to-treat response rate for both sertraline groups was 38.6%, and the completer response rate was 48.4%. The exposure-only intent-to-treat response rate was 30.6%, and the completer response rate was 33%. The combined treatment group had a trend toward significance compared with the exposure-only group ($p = 0.059$). In this primary care trial, sertraline, with or without exposure therapy, was effective in treating generalized SAD, and combined treatment was not more effective than sertraline alone.

Haug and colleagues conducted a 1-year follow-up after the termination of the 24-week treatment (2003). Of the 354 patients who were assessed at the 24-week period, 328 were evaluated 1 year later, 83 in the sertraline-plus-exposure group, 85 in the sertraline-plus-general-care group, 78 in the exposure-only group, and 82 in the placebo-plus-general-care group. All groups demonstrated a significant decrease from their baseline measures at the 1-year follow-up. The exposure-only group continued to improve from the 24-week assessment to the 1-year follow-up, with a significant change on the CGI-SP. The placebo group also showed improvement from the 24-week period to the 1-year follow-up on the CGI-SP. For the sertraline-plus-exposure and the sertraline-plus-general-care groups, there was a nonsignificant worsening on the CGI-SP at follow-up. On individual scales measuring aspects of social fear and avoidance, the exposure-only group also demonstrated continued improvement from the end of treatment to the 1-year follow-up. In addition, the placebo group demonstrated some of the same improvement, whereas there was again slight deterioration in the sertraline groups (nonsignificant).

One very important note must be considered when evaluating these data: 66 patients (20.5% of the sample) received some SSRI during the follow-up period, including those who had been assigned to a no-active-medication group. There were 13 (15.5%) in the sertraline-plus-exposure group, 18 (21.6%) in the sertraline-plus-general-care group, 14 (19.2%) in the exposure-only group, and 21 (19.5%) in the placebo group. This may account for the high rate of improvement in the placebo group and the lack of statistical significance in decreased improvement in the sertraline groups.

This RCT of generalized SAD in primary care demonstrated no greater efficacy for combined treatment than for monotherapy. There are some limitations to this research. The design did not allow for blinded evaluations of outcome; therefore, there may be some rater bias given the fact that the clinicians who conducted the treatments also made the response determinations. The exposure therapy, as conducted by physicians, differs somewhat from that conducted by trained psychiatric clinicians—the physicians directed the patients to do the exposures on their own, whereas psychiatric clinicians generally accompany the patients on many or at least some exposures, offering support and encouragement throughout the process. This often facilitates further exposures, many of which are self-directed in between

sessions. This may have accounted for the modest efficacy of exposure only.

The Blomhoff and Davidson data did not support the hypothesis that combined treatment was more effective than monotherapy in SAD, yet the Blanco study did. This difference may be attributable to the analytical method used by Blanco, an ordering or gradation of response from placebo to monotherapies to combined treatment using a linear-by-linear test. It might also be the use of a monoamine oxidase inhibitor versus an SSRI. In the Blanco study, group CBT was less efficacious than in other studies comparing monotherapies, with much lower remission rates than in the Hofmann trial described next. This lack of efficacy for group CBT is difficult to explain.

Hofmann and colleagues (2013) augmented CBT for SAD with DCS in an RCT with 169 participants at three sites, two in Boston and one in Dallas. Adults with generalized social anxiety with no history of bipolarity, psychosis, OCD, current eating disorder, substance use disorder, or PTSD were included. CBT was conducted in a group format for 12 sessions each lasting 2.5 hours. At session 3, participants were randomly assigned to 50 mg of DCS orally ($N = 87$) or pill placebo ($N = 82$) to be taken 1 hour in advance of the session. There were five exposure sessions augmented with DCS or placebo.

Measures included CGI and LSAS; response was defined as 1 or 2 on CGI-I, and remission was considered 1 or 2 on CGI plus LSAS score below 30. The response rates were 79.3% in the active group compared to 73.2% in the placebo group. The remission rates were 34.5% in the DCS group and 24.4% in the placebo group. Neither of these differences was significant. Although there was some evidence that DCS accelerated the response, by the end of treatment, there was no increased benefit for DCS in generalized SAD.

SUMMARY

According to an analysis of the national trends for outpatient treatment of anxiety disorders (Olfson, Marcus, Wan, & Geissler, 2004), the community rate of combined medication and psychotherapy treatment for any anxiety disorder was 27%, whereas the rate of combined antidepressant and psychotherapy treatment was 21%. For the most part, there is little evidence that combined psychosocial and medication therapy is superior to either alone in the treatment of mood and anxiety disorders over time. Exceptions to this are in MDD for adolescents and for those with five or more recurrent moderate to severe episodes as well as augmentation of CBT or IPT in partial responders and nonresponders.

In fact, in the case of PD and the study by Barlow and colleagues (2000), there was even evidence that adding medication to CBT impeded the success of CBT. One possible explanation for this is that long-term administration of antidepressant medication impairs learning, which interferes with the mechanism of action of CBT. This is consistent with some animal studies in which an SSRI interfered with extinction of conditioned fear learning (Burghardt et al., 2013).

Another explanation for the lack of superiority of combined treatments was suggested by Otto (2002), who postulated that medication forms a context in which learning occurs. In this case, the learning involves the gradual exposure to bodily sensations (interoceptive exposure) whereby the patient learns to be less fearful of these sensations. When the context is withdrawn, the benefit of what was learned may be diminished as well.

Although more research in the area of combined treatment for mood and anxiety disorders is surely needed, our review suggests that most patients with these disorders should be offered an evidence-based psychosocial intervention first, as these have been shown to be, for the most part, of at least equal efficacy and to have fewer adverse side effects than medication intervention. Medication would be a first-line therapy only in cases in which the patient prefers it to psychotherapy, qualified therapists are unavailable, or the severity of illness is such that more rapid onset of effect is needed. Finally, combined therapy would be used when a full course of evidence-based monotherapy is unsuccessful.

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17

Treatments for Obsessive-Compulsive Disorder

Darin D. Dougherty
Scott L. Rauch
Michael A. Jenike

There is overwhelming evidence of the most rigorous type supporting the efficacy of serotonin reuptake inhibitors (SRIs) in the treatment of obsessive-compulsive disorder (OCD). Along with SRIs, behavior therapy must be considered a viable first-line therapy. The best available data suggest that behavior therapy, and perhaps cognitive therapy, is at least as effective as medication in some instances, and may be superior with respect to risks, costs, and enduring benefits. A variety of second-line medication treatments for OCD have been studied in a controlled or systematic fashion. Augmentation of SRIs with antipsychotics, buspirone, or clonazepam is provisionally recommended based on the available data. Other monotherapies and augmentation strategies find very limited support at present.

DIAGNOSTIC CRITERIA AND CLINICAL CHARACTERISTICS

OCD is a common condition, with lifetime prevalence estimates of approximately 2% to 3% in the United States and up to 5.5% worldwide (Angst, 1994; Karno, Golding, Sorenson, & Burnam, 1988; Rasmussen & Eisen, 1994). The hallmark signs and symptoms of OCD include intrusive unwanted thoughts (i.e., obsessions) and repetitive behaviors (i.e., compulsions; American Psychiatric Association [APA], 2013). Classic obsessions include violent, religious, or sexual themes, as well as preoccupations with contamination, pathological doubting or uncertainty, concerns with symmetry, and a general sense that something bad will happen if a particular ritual is not performed in precisely the right manner. Classic compulsions include washing, cleaning, counting, checking, repeating, and arranging behaviors. For most, the disease manifests itself as multiple obsessions and multiple compulsions (Rasmussen & Eisen, 1994). Experiencing occasional unwanted thoughts, performing repetitive or ritualistic behaviors, and having transient feelings of anxiety are all part of normal human experience. However, to meet the criteria for OCD, the symptoms must be sufficiently intense or frequent to cause marked distress or impair functioning. In fact, people with OCD are often severely impaired by the symptoms of their disease. Unlike psychosis, OCD is characterized by intact insight; because people with OCD recognize that their thoughts and behaviors are extreme or nonsensical, they are often embarrassed or ashamed of their condition and frightened that they may be "going crazy." In severe cases of OCD, insight can become tenuous as obsessions progress to overvalued ideas.

The differential diagnosis of OCD includes other psychiatric disorders that are characterized by repetitive thoughts or behaviors. For instance, the obsessions of OCD are to be distinguished from the ruminations

of major depression, the racing thoughts of mania, the psychotic thoughts of schizophrenia, and the preoccupation with food and body image associated with eating disorders. Likewise, the compulsions of OCD are to be distinguished from the tics of Tourette syndrome, the ritualized self-injurious behaviors of borderline personality disorder, the rhythmic movements that can present in autism or mental retardation, and the stereotypes of complex partial seizures. By definition, the diagnosis of OCD should not be made if the symptoms can be attributed to another disorder or are the consequence of substance use (APA, 2013).

A variety of disorders within *Diagnostic and Statistical Manual of Mental Disorders* (APA, 2013) are also characterized by repetitive symptoms (Hollander, 1993, Hollander et al., 1996; McElroy, Phillips, & Keck, 1994). The classification "OCD and Related Disorders" within DSM-5 has been coined to reflect the notion that a family of similar disorders may exist that share some common phenomenological, etiological, and perhaps pathophysiological characteristics. Such related disorders include Tourette syndrome (characterized by intrusive sensations and urges, as well as a drive to perform motor and vocal tics), hair pulling disorder/trichotillomania (characterized by compulsive hair pulling), skin picking disorder (characterized by compulsive skin picking), hoarding disorder (characterized by excessive accumulation of items), and body dysmorphic disorder (characterized by a preoccupation with certain aspects of one's own appearance). Comorbidity among the related disorders with OCD is common; in addition to other related disorders, frequently coexisting conditions include major affective disorders, anxiety disorders, and substance use disorders (Karno et al., 1988; Rasmussen & Eisen, 1994).

ETIOLOGY AND NEUROBIOLOGY

Although the cause of OCD remains unknown, family genetic studies suggest that OCD is a familial disorder (e.g., Black et al., 1992; Hettema et al., 2001; Nestadt et al., 2000; Pauls et al., 1995). Specifically, family genetic studies indicate that in some cases OCD seems to arise sporadically, whereas in others there exists an apparent familial relationship. A review of OCD twin studies (van Grootheest et al., 2005) concluded that OCD is heritable, with genetic influences ranging from 45% to 65% in children and from 27% to 47% in adults. Contemporary neurobiological models implicate dysfunction in one or another of several segregated corticostriatal pathways (Dougherty, Rauch, & Greenberg, 2010; Rauch, Whalen, Dougherty, & Jenike, 1998). OCD seems to involve subtle structural abnormalities in the caudate nucleus, as well as functional dysregulation of neural circuits comprising orbitofrontal cortex, cingulate cortex, and the caudate. Some research suggests that autoimmune processes, precipitated in some cases by beta-hemolytic streptococcal infection, may cause damage to striatal neurons in occasional sporadic childhood-onset cases of OCD and Tourette syndrome (Allen, Leonard, & Swedo, 1995; Swedo 1994; Swedo, Leonard, & Kiessling, 1994; Swedo et al., 1998). Neurochemically, serotonergic systems have been implicated in OCD (Rauch et al., 1998). Of note, however, some recent imaging studies have also implicated the dopaminergic system in OCD (Denys, van der Wee, Janssen, De Geus, & Westenberg, 2004b; Denys, Zohar, & Westenberg, 2004c), which resonates with emerging evidence supporting augmentation therapy with dopaminergic antagonist medications for OCD (e.g., Denys, de Geus, van Megen, & Westenberg, 2004a; McDougle, Epperson, Pelton, Wasylink, & Price, 2000).

HISTORICAL PERSPECTIVE

Descriptions of probable OCD date back to the 15th century, and up through the 1700s the malady was conceptualized in religious or supernatural terms (Hunter & Macalpine, 1982; Pitman, 1994). Treatments such as exorcism notwithstanding, clinical reports and attempts to medically or scientifically characterize OCD did not emerge until the late 1800s, when neurologists, including Georges Gilles de la Tourette (1885), described OCD symptoms in the context of movement disorders. In the early 1900s, other clinicians contributed eloquent phenomenological descriptions of obsessive-compulsive symptoms (Janet, 1903; Meige & Feindel, 1907), but little progress was made toward effective treatment of OCD. Freud's case of the Rat Man (1909/1924) introduced the application of psychodynamic principles in attempts to both understand and relieve what he termed *obsessional neurosis*.

It was not until 1967 that the tricyclic antidepressant clomipramine, the first available SRI, emerged

as an effective treatment for OCD (Fernandez & Lopez-Ibor, 1967). Contemporaneously, behavioral therapy for OCD was emerging as a viable treatment modality and the object of formal study (Rachman, Hodgson, & Marks, 1971). Interestingly, it was also in the 1960s that Ballantine and colleagues began their pioneering efforts to systematically study the safety and efficacy of anterior cingulotomy, a neurosurgical treatment for severe treatment-refractory OCD and other psychiatric illnesses (Ballantine, Bouckoms, Thomas, & Giriunas, 1987).

The subsequent quarter-century has seen great development in the assessment and treatment of OCD. Several educational and self-help books written for lay audiences (e.g., Baer, 1991; Rapoport, 1989), articles appearing in the general medical literature (Jenike, 1989), and the birth of an advocacy group (International OCD Foundation; http://www.ocfoundation.org) all contributed to a growing awareness of OCD. Whereas it had still been believed that OCD was a relatively rare disorder (approximately 0.1% lifetime prevalence), publication of the Epidemiological Catchment Area study results (Karno et al., 1988) surprised much of the psychiatric and public health community by suggesting that OCD had a lifetime prevalence of 2.6%, ranking it as the fourth most common psychiatric illness in the United States. In 1989, a collaborative group of investigators from Yale University and Brown University published studies reporting on the validation of a scale for quantifying the severity of OCD symptoms (Goodman et al., 1989b, 1989c). The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) became the gold-standard measure for many of the clinical trials that followed. During this same era the pharmaceutical industry produced a new class of compounds known as *selective serotonergic reuptake inhibitors* (SSRIs) that, like clomipramine, acted by blocking serotonergic reuptake sites. Unlike clomipramine, however, these new SSRIs had much lower affinities for adrenergic and cholinergic receptors, presumably conferring upon them a more favorable side-effect profile. Investigators in psychopharmacology proceeded to systematically study these new agents, as well as other novel compounds, while their psychotherapist counterparts conducted investigations of cognitive and behavioral treatments. During the 1990s alone, there were more than 1,500 reports about drug treatments and OCD published in medical sources. Moreover, neuroscience advances have brought us closer to understanding the etiology and pathophysiology of OCD and related disorders.

CONTEMPORARY TREATMENT

Numerous reviews have been written regarding treatment recommendations for OCD (e.g., Dominguez & Mestre, 1994; Dougherty, Rauch, & Jenike, 2004, 2012; Goodman, McDougle, & Price, 1992; Jenike 1993a, 1993b, 1998; Jenike & Rauch, 1994; Montgomery 1994; Rauch & Jenike, 1994; Table 17.1). There is broad agreement among experts in the field that first-line treatments for OCD include SRIs (clomipramine or SSRIs) and/or behavior therapy. When these first-line interventions fail, second-line pharmacological approaches include augmentation of SRIs with additional medications or trials of alternative medications as monotherapies in place of SRIs. Third-line treatments may include experimental treatments such as unproven augmentation therapies or intravenous clomipramine if available (Fallon et al., 1992, 1998; Koran, Sallee, & Pallanti, 1997; Warneke, 1989). Finally, other nonpharmacological treatments, including deep brain stimulation (DBS), neurosurgery, and electroconvulsive therapy (ECT), have remained more controversial and are reserved for particular clinical situations or as treatments of last resort. In the following section, the scientific evidentiary basis for these various treatment recommendations is reviewed. Although the focus in this chapter is on psychopharmacology, the authors wish to explicitly emphasize that most experts view behavior therapy as a critical and effective first-line treatment for OCD, and that this brand of treatment is all too often overlooked or unavailable.

Measures of Symptom Severity and Treatment Response

Before reviewing the extensive database on clinical trials in OCD, it is worth considering the instruments available for measuring the severity of symptoms and clinical improvement. The tools for quantifying the dependent variables in these studies as well as the thresholds that are adopted to operationalize "treatment response" profoundly affect the results and interpretations of clinical research.

TABLE 17.1 Sample Treatment Recommendations for Obsessive-Compulsive Disorder

Treatment	*Dosage*	*Time Course*
First Line		
Behavior therapy		
Exposure and response prevention		At least 20 hours
Medication: Serial SRI trials (consider at least two SSRI trials and one of CMI)		
CMI	150–250 mg/day	12 weeks
Fluoxetine	40–80 mg/day	12 weeks
Sertraline	50–200 mg/day	12 weeks
Fluvoxamine	200–300 mg/day	12 weeks
Paroxetine	40–60 mg/day	12 weeks
Citalopram	40 mg/day	12 weeks
Escitalopram	20–30 mg/day	12 weeks
Second Line		
Modifications to behavior therapy		
Consider inpatient sessions; home visits or other in situ sessions; or cognitive therapy		
Medication: SRI augmentation		
Clonazepam	0.5–5 mg/day	4 weeks
Buspirone	15–60 mg/day	8 weeks
Antipsychotics		
Pimozide	1–3 mg/day	4 weeks
Haloperidol	0.5–10 mg/day	4 weeks
Risperidone	0.5–6 mg/day	4 weeks
Olanzapine	2.5–15 mg/day	4 weeks
Quetiapine	200-600 mg/day	4 weeks
Medication: Alternative monotherapies		
Clonazepam	0.5–5 mg/day	4 weeks
Buspirone	30–60 mg/day	6 weeks
Phenelzine	60–90 mg/day	10 weeks
Venlafaxine	To 375 mg/day	12 weeks
Duloxetine	To 120 mg/day	12 weeks
Third Line		
Alternative monotherapies without controlled data		
Alternative augmentation strategies without controlled data		
Fourth Line		
DBS		
Consider neurosurgery (only if OCD is longstanding, severe, debilitating, and unresponsive to an exhaustive array of other treatments)		

CMI = clomipramine; OCD = obsessive-compulsive disorder; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

As noted above, the gold-standard instrument for quantifying OCD symptom severity is the Y-BOCS (Goodman et al., 1989b, 1989c), a rater-administered scale scored from 0 to 40, with high values reflecting more severe symptoms. The Y-BOCS comprises 10 elements, 5 elements about obsessions and 5 about compulsions (i.e., frequency/time consumed, interference, distress, resistance, and control over symptoms). Each element is rated from 0 to 4. Alternative contemporary rater-administered instruments include unidimensional global scales (Pato, Eisen, & Pato, 1994). The National Institute of Mental Health Global Obsessive Compulsive Scale (NIMH-GOCS; Insel et al., 1983) is a 15-point scale that has been shown to correlate with the Y-BOCS, although the descriptive anchor points of the NIMH-GOCS tend to emphasize elements of interference and resistance. Clinical Global Improvement (CGI; see Pato et al., 1994) scales represent another type of unidimensional rater-administered instruments that are commonly used in clinical trials, such as the 7-point CGI, with anchor points including 1 = very much improved, 4 = no change, and 7 = very much worse. The rater-administered CGI has also been shown to correlate well with the Y-BOCS and NIMH-GOCS; modified versions of the CGI can be self-administered by patients. Other self-administered instruments include the Leyton Obsessional Inventory (LOI; Cooper 1970) and the Maudsley Obsessive Compulsive Inventory (MOCI; Sternberger & Burns, 1990). As inventories, both consist of symptom-related and/or trait-related questions with binary response options (i.e., yes/no or true/false). Self-ratings can be particularly problematic in OCD, which, together with the fact that these scales are limited to specific symptom sets, makes them suboptimal for characterizing symptom severity or gauging clinical improvement in treatment trials (see Kim, Dysken, & Kuskowski, 1990; Pato et al., 1994).

Typically, for studies that report a percentage of responders, criteria for response might include decrease in Y-BOCS of at least 25% or 35%, and/or a CGI of 1 or 2. Therefore, it is important to appreciate that a substantial proportion of "responders" in these studies remain symptomatic and meaningfully affected by their residual illness.

First-Line Pharmacotherapy: Serotonin Reuptake Inhibitors

Currently, the SRIs are the first-line treatment for OCD (Dougherty & Rauch, 1997; Dougherty, Rauch, & Jenike, 2012). There is overwhelming evidence from multiple randomized, double-blind, placebo-controlled studies supporting the efficacy of SRIs in the treatment of OCD (Table 17.2). Specifically, in adults, well-designed and well-controlled trials have demonstrated the relative efficacy of clomipramine versus placebo, as well as the relative efficacy of SSRIs, including fluoxetine, sertraline, paroxetine, and fluvoxamine, versus placebo. Moreover, SRIs have been shown to be significantly more effective than non-SRI tricyclic antidepressants (TCAs) in placebo-controlled as well as non–placebo-controlled studies (Table 17.3). In the only randomized, double-blind, placebo-controlled study involving non-SRI TCAs, nortriptyline was not shown to be significantly more effective than placebo (Thoren, Asberg, Cronholm, Jornestedt, & Traskman, 1980; see Table 17.2), supporting the view that non-SRI TCAs are not an effective monotherapy for OCD.

Despite a wide range of observed SRI response rates, large-scale studies have generally yielded approximately 40% to 60% responders, with mean improvement in the active treatment group of approximately 20% to 40% (see Greist et al., 1995b). In terms of the relative efficacy among SRIs, a large-scale meta-analysis of multicenter trials of SRIs was performed by Greist and colleagues (1995c) in which clomipramine (n = 520), fluoxetine (n = 355), sertraline (n = 325), and fluvoxamine (n = 320) were all shown to be significantly superior to placebo. This meta-analysis further indicated that clomipramine might have superior efficacy over SSRIs. Although the meta-analysis by Greist and colleagues had many strengths, including that all studies used comparable parameters and were conducted at essentially the same centers, the results should be interpreted with caution. Since there was a serial progression in the availability of these agents and in the performance of these trials, clomipramine was studied on an SRI-naïve population, whereas each successive agent was undoubtedly tried on a cohort comprising a larger subpopulation of patients with histories of past SRI unresponsiveness. Consequently, each successive trial might well have been conducted on a more treatment-resistant population, biasing the efficacy in favor of agents studied in earlier years (i.e., clomipramine). In fact, a growing number of studies (see Table 17.3) and a comprehensive literature review (Pigott & Seay, 1999) suggest that the SRIs all have comparable efficacy. However, despite these group data, any single individual may respond very

TABLE 17.2 Placebo-Controlled Trials of Serotonin Reuptake Inhibitor Therapy for Obsessive-Compulsive Disorder (Adults)

Treatment Conditions	*N*	*Comments*	*Study*
CMI vs. placebo	20	CMI significantly superior to placebo	Karabanow (1977)
CMI vs. placebo crossover	14	CMI significantly superior to placebo	Montgomery (1980)
CMI vs. nortriptyline vs. placebo	24	CMI, but not nortriptyline, superior to placebo	Thoren et al. (1980)
CMI vs. placebo	12	CMI significantly superior to placebo	Mavissakalian et al. (1985)
CMI vs. placebo	27	CMI significantly superior to placebo	Jenike et al. (1989)
CMI vs. placebo	32	73% improved on CMI; 6% improved on placebo	Greist et al. (1990)
CMI vs. placebo	239	38% average decrease in symptoms with CMI 3% average decrease in symptoms with placebo	CMI collaborative group (1991)
CMI vs. placebo	281	44% average decrease in symptoms with CMI 5% average decrease in symptoms with placebo	CMI collaborative group (1991)
CMI vs. placebo	36	CMI significantly superior to placebo	Foa et al. (2005)
CMI vs. venlafaxine	47/26	50% CMI responders; 36% venlafaxine responders; no statistically significant difference	Albert et al. (2002)
CMI vs. fluvoxamine	227	Both effective with no statistically significant difference	Mundo et al. (2001)
CMI vs. fluvoxamine	65/68	Both effective with no statistically significant difference	Mundo et al. (2000)
Sertraline vs. placebo	87	Sertraline significantly superior to placebo	Chouinard et al. (1990)
Sertraline vs. placebo	19	Sertraline significantly superior to placebo	Jenike et al. (1990a)
Sertraline vs. placebo	325	Sertraline significantly superior to placebo	Greist et al. (1995a)
Sertraline vs. placebo	167	Sertraline significantly superior to placebo	Kronig et al. (1999)
Sertraline vs. fluoxetine	77/73	Equivalent improvement on Y-BOCS; higher proportion of remission with sertraline	Bergeron et al. (2002)
Sertraline vs. desipramine	166	Sertraline significantly superior to desipramine	Hoehn-Saric et al. (2000)
Fluvoxamine vs. placebo	16	Fluvoxamine significantly superior to placebo	Perse et al. (1987)
Fluvoxamine vs. placebo	42	Fluvoxamine significantly superior to placebo	Goodman et al. (1989a)
Fluvoxamine vs. placebo	38	Fluvoxamine significantly superior to placebo	Jenike et al. (1990b)
Fluvoxamine vs. placebo	160	Fluvoxamine significantly superior to placebo	Goodman et al. (1996)
Fluvoxamine vs. BT vs. placebo	31	BT superior to fluvoxamine, which was superior to placebo	Nakatani et al. (2005)
Fluvoxamine CR vs. placebo	153	Fluvoxamine controlled release (CR) significantly superior to placebo	Hollander et al. (2003e)
Fluoxetine vs. placebo	355	Fluoxetine (20, 40, 60 mg) significantly superior to placebo Fluoxetine (40, 60 mg) significantly superior to placebo; 20-mg effects equal to placebo	Tollefson et al. (1994b)

TABLE 17.2 (continued)

Treatment Conditions	*N*	*Comments*	*Study*
Fluoxetine vs. placebo	217	Paroxetine (40, 60 mg) significantly superior to placebo; 20-mg effects	Montgomery et al. (1993)
Paroxetine vs. placebo	348	equal to placebo	Wheadon et al. (1993)
Paroxetine vs. venlafaxine	75/75	Equally efficacious	Denys et al. (2003)
Citalopram vs. placebo	401	Citalopram (20, 40, 60 mg) significantly superior to placebo	Montgomery et al. (2001)
Escitalopram vs. paroxetine vs. placebo	466	Escitolpram (20 mg, 10 mg) & paroxetine (40 mg) significantly superior to placebo	Stein et al. (2007)

BT = behavior therapy; CMI = clomipramine.

well to one or two agents of the SRI medications and not the others. Thus, serial trials of each agent may be required to determine which drug is best.

Data regarding duration of treatment, optimal dose, and adverse side effects are also plentiful but difficult to interpret with confidence because studies were often not designed to specifically answer these questions. The collective wisdom, purportedly supported by the data from the multicenter trials as well as anecdotal clinical experience, has been that response to SRIs is typically delayed such that an adequate trial of an SRI requires at least 10 weeks' duration. Indeed, a meaningful proportion of responders continue to emerge past the 8-week mark in these studies, as well as in anecdotal clinical experience. Experts also suggest that optimal doses of SRIs for OCD may exceed those typically used for major depression (e.g., Montgomery et al., 1993), although the dose-comparison studies of OCD have not always shown significant dose-dependent responses across the OCD study population (e.g., Greist et al., 1995a). As for adverse side effects, although the meta-analysis by Greist and colleagues (1995c) did not find any significant difference between medication groups regarding dropout rates due to adverse side effects, this is a relatively insensitive measure of adverse side-effect profile. Also, the aforementioned cohort effects apply for adverse side effects as well; subjects participating in the early clomipramine trials may have viewed that agent as the only available course of treatment, whereas subjects in later SSRI trials may have been aware of the wider variety of available treatments, making them less willing to endure nuisance adverse side effects. Clearly, as with other TCAs, the risks and adverse side effects mediated by anticholinergic and antiadrenergic mechanisms (e.g., constipation, cardiac conduction disturbances, orthostatic hypotension) are more commonly associated with clomipramine than with SSRIs. Furthermore, clomipramine is believed to pose a significant risk with regard to lowering seizure threshold. All SRIs can pose risks (e.g., serotonergic syndrome) and produce a variety of adverse side effects (e.g., nausea, sleep disturbances, sexual disturbances) attributable to their primary mechanism of action via serotonergic reuptake blockade (Grimsley & Jann, 1992). There is no substantive evidence that any SRI is significantly superior or inferior to any other with regard to serotonergically mediated adverse side effects.

Although many clinicians use SRIs as a long-term treatment for OCD, few controlled studies of long-term pharmacotherapy of OCD have been conducted. While most open studies have demonstrated high relapse rates of OCD symptoms within weeks of discontinuation (Pato, Zohar-Kaduch, Zohar, & Murphy, 1988; Thoren et al., 1980), one open-label study of SRI discontinuation found that only 23% of patients relapsed within 1 year (Fontaine & Chouinard, 1989). One randomized, double-blind study incorporating substitution of desipramine for clomipramine in a crossover design found that 89% of patients in the substituted group encountered relapse during a 2-month period (Leonard et al., 1991). More

TABLE 17.3 Non–Placebo-Controlled Trials of Drug Therapy for Obsessive-Compulsive Disorder (Adults)

Treatment Conditions	*N*	*Comments*	*Study*
CMI vs. amitriptyline	20	CMI significantly superior to amitriptyline	Ananth et al. (1981)
CMI vs. amitriptyline	39	95% improved on CMI 56% improved on amitriptyline	Zhao (1991)
CMI vs. clorgyline	13	CMI effective; clorgyline ineffective	Insel et al. (1983)
CMI vs. clorgyline	12	CMI superior to clorgyline	Zahn et al. (1984)
CMI vs. doxepin	32	78% markedly improved on CMI 36% markedly improved on doxepin	Cui (1986)
CMI vs. fluvoxamine	6	Comparable efficacy	Den Boer et al. (1987)
CMI vs. fluvoxamine	66	Comparable efficacy	Freeman et al. (1994)
CMI vs. fluvoxamine	79	Comparable efficacy	Koran et al. (1996)
CMI vs. fluvoxamine	26	Comparable efficacy	Milanfranchi et al. (1997)
CMI vs. fluvoxamine	133	Comparable efficacy	Mundo et al. (2000)
CMI vs. fluoxetine	11	Comparable efficacy	Pigott et al. (1990)
CMI vs. fluoxetine	55	Comparable efficacy	Lopez-Ibor et al. (1996)
CMI vs. imipramine	16	CMI superior to imipramine	Volavka et al. (1985)
CMI vs. imipramine crossover	12	CMI superior to imipramine	Lei (1986)
CMI vs. paroxetine	406	Comparable efficacy	Zohar et al. (1996)
CMI vs. sertraline	168	Comparable efficacy (fewer dropouts with sertraline)	Bisserbe et al. (1995)
Fluvoxamine vs. desipramine	40	Fluvoxamine superior to desipramine	Goodman et al (1990)
Fluvoxamine vs. paroxetine vs. citalopram	30	Comparable efficacy	Mundo et al. (1997b)
Citalopram	29	76% improved in 24-week open-label trial	Koponen et al. (1997)
Citalopram	18	14 of 18 showed reduced Y-BOCS score in open-label trial	Marazziti et al. (2001)
Venlafaxine	39	69% improved in open-label trial	Hollander et al. (2003c)

Source: Adapted from Jenike, 1998.

CMI = clomipramine.

recently, four placebo-controlled relapse-prevention studies have been conducted. One study assigned responders to fluoxetine to either continued treatment with fluoxetine ($n = 36$) or placebo ($n = 35$) and found 1-year relapse rates of 17.5% and 38%, respectively (Romano, Goodman, Tamura, & Gonzales, 2001). Another study assigned responders to sertraline to either continued treatment with sertraline or placebo and found relapse rates of 21% versus 59%, respectively (Koran, Hackett, Rubin, Wolkow, & Robinson, 2002). One study found that paroxetine responders assigned to continued treatment with paroxetine or placebo exhibited relapse rates of 38% versus 59%, respectively (Hollander et al., 2003a). Lastly, one study found that escitalopram responders assigned to continued treatment with escitalopram or placebo exhibited relapse rates of 23% versus 52%, respectively, at 24 weeks (Fineberg et al., 2007). Some investigators have proposed using lower doses of SRIs for OCD maintenance treatment based on open-label trials (Pato, Hill, & Murphy, 1990; Ravizza, Barzega, Bellino, Bogetto, & Maina, 1996), and two controlled studies have demonstrated the efficacy of this approach (Mundo et al., 1997a; Tollefson, Birkett, Koran, & Genduso, 1994a). Thus, the data suggest that discontinuing SRIs in patients with OCD

results in a high relapse rate, although there is still some debate regarding maintenance dosages of SRIs.

In addition to the above data regarding pharmacotherapy for OCD in adults, there are analogous studies in children and adolescents documenting the efficacy of CMI over non-SRI TCAs as well as placebo (Table 17.4). There are a number of placebo-controlled studies of SSRIs for OCD in children, which likewise support the efficacy of SRIs in treating OCD in children. A meta-analysis suggests that clomipramine may be superior to the SSRIs in treating pediatric OCD (Geller et al., 2003).

Second-Line Pharmacotherapy: Serotonin Reuptake Inhibitor Augmentation and Alternative Monotherapies

For patients who do not derive satisfactory reduction of symptoms with SRI therapy, second-line pharmacological treatments include SRI augmentation and alternative monotherapies. It is important to appreciate that only a minority of patients with OCD do not respond favorably to SRIs and that this relatively treatment-resistant group may be quite heterogeneous, including with respect to underlying pathophysiology. Therefore, specific subsequent treatments may be very effective for some subset of this population while having only modest mean efficacy for the overall cohort. Consequently, some second-line treatment trials have focused on the number or proportion of patients who meet responder criteria rather than the mean decrease in symptom severity over the entire study population. Moreover, in some instances, attention has been focused on the clinical characteristics that might distinguish responders from nonresponders.

Augmentation of Serotonin Reuptake Inhibitors

Numerous agents have been tried as augmenting agents in combination with SRIs for patients who were unresponsive or only partially responsive to SRIs alone (see Dougherty et al., 2004; Jenike, 1998; McDougle & Goodman, 1997). However, few controlled trials of such strategies have been conducted (Table 17.5). Despite numerous case reports

TABLE 17.4 Controlled Trials of Serotonin Reuptake Inhibitor Therapy for Obsessive-Compulsive Disorder (Children and Adolescents)

Treatment Conditions	*N*	*Comments*	*Study*
CMI vs. desipramine vs. placebo	8 adolescents	No significant differences crossover	Rapoport et al. (1980)
CMI vs. placebo cross-over	14 children	CMI superior to placebo	Flament et al. (1985a, 1985b)
CMI vs. desipramine	48	CMI superior to desipramine; 64% of patients relapsed when desipramine substituted for CMI	Leonard et al. (1988)
CMI substituted with desipramine in half of subjects	26	89% receiving desipramine relapsed 18% remaining on CMI relapsed	Leonard et al. (1991)
CMI vs. placebo	61	37% average decrease with CMI 8% average decrease with placebo	DeVeaugh-Geiss et al. (1992)
Fluoxetine vs. placebo	14 children	Fluoxetine superior to placebo	Riddle et al. (1992)
Sertraline vs. placebo	187	Sertraline superior to placebo	March et al. (1998)
Fluoxetine vs. placebo	43	Fluoxetine superior to placebo	Liebowitz et al. (2002)
Fluoxetine vs. placebo	103	Fluoxetine superior to placebo	Geller at al. (2001)
Sertraline, BT, combination of sertraline and BT, or placebo	112	Combined > BT = sertraline > placebo	POTS Team (2004)
Fluvoxamine vs. placebo	120	Fluvoxamine superior to placebo	Riddle et al. (2001)

Source: Adapted from Jenike 1998.

CMI = clomipramine.

TABLE 17.5 Serotonin Reuptake Inhibitor Augmentation Therapies for Obsessive-Compulsive Disorder: Controlled Trials

Augmenting Agent	*SRI*	*N*	*Trial*	*Results*	*Study*
Lithium	Fluvoxamine	30	2- or 4-week double-blind placebo-controlled	Very little improvement	McDougle et al. (1991)
Lithium	CMI	9	Double-blind crossover (with T3)	None	Pigott et al. (1991)
L-triiodo-thyronine (T3)	CMI	9	Double-blind crossover (with lithium)	None	Pigott et al. (1991)
Buspirone	CMI	14	2-week placebo, then 10-weeks buspirone	4/14 (29%) improved an additional 25% on buspirone; 3/14 (21%) worsened >25% on depression scores	Pigott et al. (1992a)
Buspirone	Fluoxetine	14	Double-blind crossover with placebo; 4 weeks per treatment condition	1/14 (7%) improved significantly more with buspirone	Grady et al. (1993)
Haloperidol	Fluvoxamine	34	Double-blind placebo-controlled, with 17 per group; 4-week trial; after failing fluvoxamine alone	11/17 (65%) responded to haloperidol; 0/17 to placebo; 8/8 with tics responded to haloperidol	McDougle et al. (1994)
Clonazepam	CMI or fluoxetine	16	Placebo-controlled, crossover; 4-week trial; after 20-week stable dose on CMI or fluoxetine	Significant improvement in OCD on one of three measures for clonazepam vs. placebo; significant improvement in global anxiety as well	Rauch & Jenike (1994)
Clonazepam	Sertraline	37	Placebo-controlled,	No significant difference	Crockett et al. (2004)
Pindolol	Paroxetine	14	Double-blind, placebo-controlled, 4-week trial after ~17 weeks stable dose of paroxetine	Significant ($p<0.01$) improvement in YBOCS	Dannon et al. (2000)
Risperidone	SRI	36	Double-blind, placebo-controlled; 6-week trial after 12 weeks on SRI	50% responders; significant ($p < .001$) reduction in Y-BOCS	McDougle et al. (2000)
Risperidone	SRI	16	Double-blind, placebo-controlled; 8-week trial after at least 12 weeks on SRI	40% responders	Hollander et al. (2003b)
Risperidone	SRI	16	Double-blind, placebo-controlled; 2-week crossover trial with haloperidol	Both risperidone and haloperidol superior to placebo	Li et al. (2005)

TABLE 17.5 (continued)

Augmenting Agent	*SRI*	*N*	*Trial*	*Results*	*Study*
Olanzapine	Fluoxetine	44	Placebo controlled; 6-week trial after 8 weeks on fluoxetine	No significant difference	Shapira et al. (2004)
Olanzapine	SRI	26	Double-blind, placebo-controlled; 6-week trial	Significant improvement of Y-BOCS	Bystritsky et al. (2004)
Quetiapine	SRI	40	Double-blind, placebo-controlled; 8-week trial	Quetiapine superior to placebo	Denys et al. (2004a)
Quetiapine	SRI	42	Double-blind, placebo-controlled, 6-week trial	No significant difference between quetiapine and placebo	Carey et al. (2005)
Quetiapine	SRI	27	Single-blind, placebo-controlled; 8-week trial	9/14 in active group had 60% or greater decrease in Y-BOCS score; no improvement with placebo	Atmaca et al. (2002)
Quetiapine	SRI	76	Double-blind, placebo-controlled, 10-week trial	Quetiapine superior to placebo	Vulink et al. (2009)
Quetiapine	SRI	40	Double-blind, placebo-controlled, 12-week trial	No significant difference between quetiapine and placebo	Kordon et al. (2008)

CMI = clomipramine; SRI = serotonin reuptake inhibitor.

suggesting that lithium might be an effective augmenting agent in combination with various SRIs, the only two controlled trials of lithium, added to fluvoxamine (McDougle et al., 1991) and clomipramine (Pigott et al., 1991), respectively, speak against the efficacy of these combinations.

Similarly, the encouraging results from case series and uncontrolled trials of buspirone augmentation (see Dougherty et al., 2004; Jenike, 1998; McDougle & Goodman, 1997) were followed by only marginal success in controlled trials. In Pigott and colleagues' (1982) study of buspirone plus clomipramine, despite a 29% responder rate, there was not significant improvement over the entire cohort with respect to OCD symptoms, and 3 of 14 subjects experienced an exacerbation of more than 25% on measures of depression, for unclear reasons. In Grady and colleagues' (1993) double-blind crossover study of buspirone augmentation of fluoxetine, only 1 of 14 subjects showed improvement, which may have reflected the brief duration of treatment (only 4 weeks in each phase). Finally, McDougle and colleagues (1993b) found greater improvement with placebo than with buspirone in a double-blind, placebo-controlled study of buspirone augmentation of fluvoxamine for 6 weeks.

Contrary to a small case series reporting unimpressive results (Jenike, 1998), the use of clonazepam as an augmenting agent with clomipramine or fluoxetine has been studied in a placebo-controlled fashion, with some studies suggesting significant antiobsessional efficacy as well as a nonspecific decrease in anxiety measures (Pigott, L'Heueux, Rubenstein, Hill, & Murphy, 1992b; see Rauch & Jenike, 1994) and another study finding no significant difference when compared with placebo (Crockett, Churchill, & Davidson, 2004).

The most impressive augmentation data document the benefits of adding low doses of dopamine antagonists (both first-generation and second-generation antipsychotic medications) to SRI pharmacotherapy in patients with

treatment-refractory OCD (McDougle et al., 1990, 1994, 2000). Some data (McDougle et al., 1993a) initially suggested that OCD patients with comorbid tics may be less responsive to SRI monotherapy than OCD patients without tics. More recent studies have demonstrated the efficacy of SRI augmentation with antipsychotics in OCD patients with and without comorbid tics (McDougle et al., 2000). Although initial studies demonstrated the efficacy of SRI augmentation with first-generation antipsychotics, more recent controlled studies of augmentation with second-generation antipsychotics have yielded encouraging results as well. Three controlled trials of risperidone augmentation of an SRI (Hollander, Baldini, Rossi, Sood, & Pallanti, 2003; Li et al., 2005; McDougle et al., 2000) demonstrated efficacy. Of two controlled trials of olanzapine augmentation, one study (Bystritsky et al., 2004) yielded positive results but the other (Shapira et al., 2004) did not. Finally, three controlled studies (Atmaca, Kuloglu, Tezcan, & Gecici, 2002; Denys et al., 2004a; Vulink et al., 2009) of quetiapine augmentation yielded positive results, while two others (Carey et al., 2005; Kordon et al., 2008) did not. It is worth mentioning that, although second-generation antipsychotics are efficacious as SRI augmentation agents, they are ineffective when used as monotherapy and may even precipitate or worsen OCD symptoms when used as monotherapy (for review, see Lykouras et al., 2003)

Numerous other agents have been tried in combination with SRIs, including clonidine, tryptophan, fenfluramine, pindolol, riluzole, trazodone, and nortriptyline, as well as other antidepressants (see Dougherty et al., 2004; Jenike, 1998; McDougle & Goodman, 1997, for reviews). The small number of subjects, lack of sufficient controls, and mixed results preclude drawing even preliminary conclusions regarding the potential efficacy of such strategies. If an augmenting agent is indicated for treatment of some comorbid condition (e.g., lithium for bipolar disorder, trazodone for insomnia, or clonidine for Tourette syndrome) and no strong contraindication is present, then a trial of the agent in combination with an SRI is easily rationalized. Anecdotally, these strategies have appeared to be of tremendous benefit in some isolated cases. No studies have sought to establish the optimal dosage or duration of treatment for any of these augmentation strategies. Therefore, current guidelines reflect the parameters used in the reported successful trials, as well as anecdotal experience with OCD and other psychiatric disorders.

Alternative Monotherapies

For patients who fail to derive satisfactory response from trials of SRIs alone as well as augmentation strategies, the next recommended step is to consider alternative monotherapies in place of SRIs. In addition to uncontrolled data, positive controlled studies lend some support for trials of clonazepam, monoamine oxidase inhibitors (MAOIs), and buspirone (Table 17.6).

In the case of clonazepam, one placebo-controlled study (Hewlett, Vinogradov, & Agras, 1992) supports its efficacy in OCD, and another placebo-controlled study failed to demonstrate efficacy in OCD (Hollander, Kaplan, & Stahl, 2003). If clonazepam is used as a monotherapy for OCD, recommendations regarding dosage (i.e., 0.5 to 5 mg/day) and duration (i.e., 4 weeks or longer) have no controlled empirical basis and are simply extrapolated from clinical experience with benzodiazepines for other anxiety disorders and these few reports in OCD.

Non–placebo-controlled studies involving the MAOI clorgyline speak against its efficacy in OCD, showing no significant decrease in OCD severity (Insel et al., 1983) and inferior efficacy in comparison to SRIs (Insel et al., 1983; Zahn, Insel, & Murphy, 1984). In contrast, small case series suggested beneficial results from the MAOI phenelzine in patients with comorbid OCD and panic disorder (Jenike, Surman, Cassem, Zusky, & Anderson, 1983). A non–placebo-controlled study of phenelzine versus clomipramine suggested significant clinical improvement in both groups and no significant difference in efficacy between the two agents (Vallejo et al., 1992). The results of Vallejo and colleagues must be interpreted with caution, however, since the study was underpowered to identify a difference between clomipramine and phenelzine, and suboptimal clinical measures of improvement were employed. In fact, a subsequent placebo-controlled trial of phenelzine and fluoxetine demonstrated that patients treated with fluoxetine improved significantly more than those in the placebo or phenelzine groups (Jenike et al., 1997). This study did note that a subgroup of patients with symmetry obsessions did respond to phenelzine, however. Therefore, the efficacy of

TABLE 17.6 Alternative Medications as Monotherapies for Obsessive-Compulsive Disorder: Controlled Trials

Treatment Conditions	*N*	*Comments*	*Study*
Clorgyline vs. CMI	13	Clorgyline ineffective; CMI effective	Insel et al. (1983)
Clorgyline vs. CMI	12	Clorgyline inferior to CMI	Zahn et al. (1984)
Phenelzine vs. CMI	30	Both effective and comparable	Vallejo et al. (1992)
Clonazepam vs. CMI vs. Clonidine vs. active placebo crossover	25	35% average decrease with clonazepam; clonazepam comparable to CMI and superior to active placebo	Hewlett et al. (1992)
Clonazepam vs. placebo	27	No significant difference	Hollander et al. (2003d)
Buspirone vs. CMI crossover	20	Both effective and comparable, 20% improvement in 55% in both groups	Pato et al. (1991)
Fluoxetine vs. phenelzine vs. placebo	64	Fluoxetine group improved significantly more than phenelzine or placebo groups	Jenike et al. (1997)
Trazodone vs. placebo	21	No significant difference	Pigott et al. (1992b)

CMI = clomipramine.

phenelzine as a monotherapy for OCD should be regarded as provisional. Specific recommendations regarding dosage (i.e., phenelzine 60 to 90 mg/day) have little empirical basis, reflecting extrapolation from clinical practice with MAOIs for major depression and panic disorder; the duration of trials (i.e., 4 weeks or longer) mirrors that of SRIs for OCD. In addition to the usual low-tyramine diet and other precautions typically indicated in the context of an MAOI trial, it is critical to be cautious regarding the transition from serotonergic medications to an MAOI due to the risks of dangerous interactions, including serotonergic crisis. Current guidelines are based primarily on the half-life of the agents involved rather than direct empirical data related to adverse events per se. Conservative recommendations are washout periods of at least 2 weeks when transitioning from clomipramine or a short-half-life SSRI to an MAOI, at least 5 weeks when transitioning from fluoxetine to an MAOI, and at least 2 weeks when transitioning from phenelzine to an SRI.

Although one open trial of buspirone did not yield significant antiobsessional benefit (Jenike & Baer, 1988), a controlled trial of buspirone versus clomipramine suggested that both were comparably effective (Pato et al., 1991). The relatively short duration of the trial, the modest power for detecting a difference between treatments, and the absence of a placebo group mitigate against drawing firm conclusions from Pato and colleagues' study. Still, given the excellent tolerability of buspirone, other circumstantial evidence of possible efficacy as an augmenting agent, and its general efficacy as an anxiolytic, the clinical use of buspirone as an alternative monotherapy for cases of treatment-resistant OCD seems justified pending further information. Specific recommendations regarding dosage (i.e., up to 60 mg/day) and duration of trials (i.e., 6 weeks or longer) have little empirical basis, simply reflecting the protocol adopted in the study by Pato and colleagues.

Because the serotonin-norepinephrine reuptake inhibitors (SNRIs; venlafaxine, desvenlafaxine, and duloxetine) have serotonin reuptake inhibition properties, one would expect that the SNRIs might be efficacious in the treatment of OCD. However, no controlled studies of SNRIs for the treatment of OCD have been reported. A recent review of the literature (Dell'Osso et al., 2006) finds that the data that are available suggest that SNRIs seem to be as effective as SRIs in treating OCD. Nonetheless, controlled trials are needed.

Another exciting target for OCD pharmacology is the glutamatergic system (for review, see Pittenger et al., 2006). Some preliminary findings worthy of mention include small trials of positive results with memantine (Aboujaoude et al., 2009; Feusner et al., 2009), as well as riluzole (Pittenger et al., 2008). Agents targeting opioid receptors have shown promise as well, including a short report of tramadol (Goldsmith, Shapira, & Keck, 1999), as well as a controlled trial suggesting that oral morphine may

be effective for treating refractory OCD (Koran et al., 2005). Lastly, controlled trials have failed to demonstrate the efficacy of trazodone (Pigott et al., 1992a), clonidine (Hewlett, Vinogradov, & Agras, 1992), and diphenylhydramine (Hewlett et al., 1992) as monotherapies for OCD.

Nonpharmacological Therapies

Behavior Therapy

The gold-standard mode of behavior therapy for OCD is exposure and response prevention. This entails the patient actually being exposed to provocative stimuli (e.g., touching a "contaminated" object) and refraining from carrying out his or her usual compulsions (e.g., hand washing)—that is response prevention. It appears that in vivo exposure and response prevention represent the salient elements of effective behavior therapy regardless of setting, supervision, or addition of cognitive techniques.

There are numerous partially controlled trials of exposure and response prevention behavior therapy that have consistently shown impressive antiobsessional efficacy, with improvement in 75% to 85% of patients but with dropout rates as high as 20% to 30% (Foa, 2010; Simpson et al., 2006). Follow-up studies suggested that treatment gains were maintained for up to 1 to 5 years after discontinuation of active treatment, although these results were confounded by occasional "booster" sessions (Marks, 1981; Marks et al., 1975; Mawson, Marks, & Ramm, 1982). A meta-analysis (Christensen, Hadzi-Pavlovic, Andrews, & Mattick, 1987; Quality Assurance Project, 1985) based on data from 38 studies between 1961 and 1984 found comparable effect sizes for clomipramine (1.7) and behavior therapy (1.8) at the end of treatment; the benefits from exposure and response prevention persisted at a mean 80-week follow-up (effect size = 1.7), whereas no such follow-up data were available for clomipramine. In contrast, psychosurgery resulted in an effect size of 1.4 and dropped to 1.0 at the 60-week follow-up. In a separate study, Pato and colleagues (1988) showed that almost 90% of patients who received clomipramine for OCD relapsed after discontinuation of the medication. Thus, pending well-controlled head-to-head studies, based on partially controlled data and the limited method of meta-analysis, the implication is that in comparison with clomipramine or psychosurgery, behavior therapy may produce the highest mean effect size and the most enduring gains following discontinuation of active treatment.

Only a small number of studies directly comparing behavior therapy and medication have been reported. Rachman and colleagues (1979) found behavior therapy to significantly outperform clomipramine and did not find significant incremental benefit from the two treatments in combination. This study is limited, however, in that the clomipramine condition entailed relatively low doses (mean, 164 mg/day; maximum, 225 mg/day) as well as inadequate duration of clomipramine treatment (6 weeks). In another head-to-head comparison of behavior therapy and clomipramine, medication was found to be more effective for reducing obsessional doubt, whereas behavior therapy was more effective for reducing compulsive rituals (Solyom & Sookman, 1977). In practice, medication and behavior therapy are routinely used in concert, and experts in the field have long recommended this as an optimal treatment approach (e.g., Baer & Minichiello, 1990; Rauch & Jenike, 1994). Numerous studies (Honagen et al., 1998, Marks, Stern, Mawson, Cobb, & McDonald, 1980; Marks et al., 1988; O'Connor et al., 1999) have demonstrated that the combination of behavioral therapy and medication is more effective than either treatment alone, whereas two studies (Foa et al., 2005; van Balkom et al., 1998) found that the addition of SRIs to patients being treated with either cognitive therapy or exposure and response prevention was not superior to either cognitive therapy or exposure and response prevention used in patients not taking medication.

Beyond exposure and response prevention, limited trials of alternative behavioral methods have supported the use of imaginal flooding for checkers (Steketee, Foa, & Grayson, 1982) and "thought stopping" for patients with pure obsessions (Rimm & Masters, 1974). Moreover, cognitive therapy can also be effective for OCD (see Abramowitz, Taylor, & McKay, 2005). Finally, although controlled data are not currently available regarding cognitive-behavioral therapy for OCD in children and adolescents, preliminary findings of open trials and case reports suggest that, with age-appropriate modifications to the

regimen, results can be comparable to those in adults (Franklin et al., 1998; March, 1995; March, Mulle, & Herbel, 1994; Scahill, Vitulano, Brenner, Lynch, & King, 1996).

Deep Brain Stimulation

DBS, which uses surgically implanted electrodes that may be turned on and off to stimulate or inhibit activity in surrounding brain tissue, has been used for decades to treat neurological diseases such as Parkinson's disease and intractable pain (Devinsky, Beric, & Dogali, 1994). The first use of DBS for psychiatric illness reported that three out of four patients with intractable OCD were clinically improved following DBS in which the electrodes were directed at the same target as that used for neurosurgical anterior cingulotomy (see below), specifically in the anterior limb of the internal capsule (Nuttin et al., 1999). Subsequently, the worldwide experience regarding the efficacy of DBS for the treatment of OCD (see Greenberg et al., 2010) has been reported as the target migrated posteriorly to the current DBS target, the ventral capsule/ventral striatum (VC/VS). The worldwide data demonstrated that 67% to 75% patients with OCD who had not significantly improved with all conventional treatments did ultimately respond to DBS at the VC/VS target. These data resulted in U.S. Food and Drug Administration approval of DBS at the VC/VS target for treatment-refractory OCD in 2009.

Neurosurgery

Despite a large body of uncontrolled data reporting antiobsessional benefits from a variety of neurosurgical procedures (see Cosgrove & Rauch, 1995; Jenike, Rauch, Baer, & Rasmussen, 1998; Mindus et al., 1994, for reviews), thus far ethical factors and technical limitations have precluded the performance of sham-controlled studies to definitively establish the efficacy of these strategies. Neurosurgical treatment of OCD is reserved for patients with severe and debilitating illness who have failed to respond to an exhaustive array of other available treatment options and who provide informed consent or assent. Currently, the most commonly employed neurosurgical treatments for OCD include anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy, and limbic leukotomy. In recent prospective trials of cingulotomy and capsulotomy, almost half of patients experienced symptom reduction of at least 35% (Dougherty et al., 2002; Mindus et al., 1994; Sheth et al., 2013). Studies directly comparing the relative efficacy and safety among the different neurosurgical approaches are also lacking. Adverse effects, in the context of contemporary techniques, include seizure and transient headache. Perhaps surprisingly, discernible adverse effects on cognition or personality are rare (see Corkin 1980; Jenike et al., 1998; Mindus et al., 1994). With the advent of innovative surgical devices that allow functional neurosurgery without craniotomy (e.g., by gamma knife), the performance of ethical double-blind sham-controlled trials of neurosurgery for OCD is now feasible.

Electroconvulsive Therapy

There are no controlled data regarding the efficacy of ECT for OCD. Given the high comorbidity of major affective illness in OCD, and the well-established efficacy of ECT for major depression, it is not surprising that some patients with OCD have reportedly shown clinical improvement with ECT. Several limited case series and anecdotal reports suggest that ECT may be useful in some circumstances, and such intervention would seem prudent in cases where ECT is indicated based on the presence of comorbid severe affective illness (see Jenike & Rauch, 1994). Controlled data are needed, however, before meaningful conclusions can be drawn regarding the specific antiobsessional efficacy of ECT for OCD. In this regard, important considerations include the effects of ECT on patients with OCD in the absence of major depressive disorder, the careful clinical distinction between genuine OCD versus ruminations or intrusive thoughts due to a different diagnosis, and the use of clinical instruments to tease apart antidepressant effects versus antiobsessional effects versus global improvement. Currently available data do not provide compelling support for the use of ECT in OCD without comorbid ECT-responsive conditions.

NEW HORIZONS AND FUTURE TREATMENTS

Future OCD treatment research can be divided into two categories: (a) initiatives to assess and optimize

the use of currently available treatments and (b) initiatives to develop new treatments. As documented by the above review, there is much work to be done in establishing the efficacy of various treatments, following up on preliminary data with well-controlled prospective trials. Moreover, optimal doses and durations for various treatments need to be determined empirically and in a scientifically rigorous fashion. Clinical subtyping or characterization based on symptom dimensions may uncover important predictors of treatment response (Ackerman, Greenland, Bystritsky, Morgenstern, & Katz, 1994; Mataix-Cols, Marks, Greist, Kobak, & Baer, 2002; Mataix-Cols, Rauch, Manzo, Jenike, & Baer, 1999; Ravizza, Barzega, Bellino, Bogetto, & Maina, 1995), informing patients and clinicians which treatments should be tried first or avoided in particular cases. Public policy issues regarding treatment access loom large for mental health care delivery in the United States. Education of health care consumers, as well as policymakers and clinicians, will be critical to high-quality care in the years ahead. Primary care physicians must be informed about OCD, and trends in training must be established to ensure an adequate supply of therapists with expertise in behavioral methods. Technological innovations, such as telepsychiatry, may help to provide specialized assessment and treatment to remote regions and ultimately reduce the costs of care (Baer, 1991; Baer et al., 1995).

Truly novel treatments for OCD may emerge from advances in our understanding of its pathophysiology or serendipitously. As new compounds become available that interact with the serotonergic and dopaminergic systems via specific receptor subtypes (e.g., 5HT1D, 5HT1A, or 5HT3; Swerdlow, 1995), it is likely that several will be antiobsessional candidates. Beyond monoaminergic systems, agents that modulate neuropeptidergic transmission may represent the next wave of psychopharmacological agents to be tested in OCD and related disorders. For instance, we have proposed that, based on the neurochemistry of corticostriatal pathways, substance P antagonists might serve as potent antiobsessionals (Rauch et al., 1998). Such compounds are already available within the pharmaceutical industry but currently are being studied only for other indications. The hypothalamic neuropeptide oxytocin is also the subject of intensive study because of its purported role in species-specific grooming behaviors (Leckman et al., 1994). Beyond neuropharmacology, research regarding autoimmune-mediated causes of OCD have prompted investigation of plasmapheresis to clear autoantibodies plus prophylactic antibiotic treatment to prevent subsequent infections and further damage (Allen et al., 1995; Swedo, 1994; Swedo et al., 1994). Also, transcranial magnetic stimulation, which has shown promise as an alternative treatment for major depression, is being studied for use in OCD. Finally, neuroimaging studies have documented consistent brain activity changes following successful treatment with either SRIs or behavior therapy (Baxter et al., 1992; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996). Such findings underscore the potential power of neuroimaging methods in searching for predictors of treatment responsiveness.

SUMMARY

The past 40 years have seen tremendous advances in the treatment and understanding of OCD, with a recent acceleration of progress. It is now appreciated that OCD is a common disorder, and effective treatments, including medication, behavior therapy, and neurosurgery, have emerged. There is overwhelming evidence of the most rigorous type supporting the efficacy of SRIs in the treatment of OCD. Along with SRIs, behavior therapy must be considered a viable first-line therapy. The best available data suggest that behavior therapy, and perhaps cognitive therapy, is at least as effective as medication in some instances and may be superior with respect to risks, costs, and enduring benefits. A variety of second-line medication treatments for OCD have been studied in a controlled or systematic fashion. Augmentation of SRIs with clonazepam or buspirone and augmentation with high-potency antipsychotics in cases of a comorbid tic disorder are provisionally recommended based on the marginal available data. Other augmentation strategies find very limited support at present. Alternative monotherapies, including buspirone, clonazepam, and phenelzine, have all been the subject of positive controlled or partially controlled studies. However, the quality of these data make recommendations for these strategies tentative as well, pending additional information. Beyond second-line treatments, the current database is inadequate for making difficult treatment decisions. There is now considerable clinical experience with neurosurgery for severe, debilitating,

treatment-refractory OCD. The apparent modest success rates with neurosurgery and its relative safety based on open trials would seem to pose a reasonable option for a small number of cases. Still, controlled data on neurosurgery are sorely needed. The future of OCD treatment will, we hope, entail rigorous research to more clearly establish the efficacy and safety of preexisting treatment options, as well as a refined sense of which patients might respond preferentially to which interventions, at what dose, and after how long. Furthermore, we can look forward to emerging novel treatment strategies that might include modified cognitive-behavioral therapies; new compounds acting via serotonergic, dopaminergic, or neuropeptidergic systems; and interventions that counteract autoimmune processes.

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18

Psychosocial Treatments for Posttraumatic Stress Disorder

Lisa M. Najavits
Melissa L. Anderson

The study of psychosocial treatments for posttraumatic stress disorder (PTSD) has improved substantially in the past decade, with greater rigor, expansion of sampling, and diverse treatment models. It is clear that PTSD treatments work better than treatment as usual; average effect sizes are in the moderate to high range. A variety of treatments have been established as effective, with no one treatment having superiority, and both present-focused and past-focused models work (neither consistently outperforms the other). Areas of future direction include training, dissemination, client access to care, optimal delivery modes, and mechanisms of action. Methodological issues are also discussed, including improving research reporting, broadening study samples, and greater use of active comparison conditions.

CONTEXT

Awareness of PTSD has increased markedly. Its origins in the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* began in the first edition as "gross stress reaction" (American Psychiatric Association [APA], 1952), and it was eventually termed PTSD in the third edition (APA, 1980). First understood as a disorder primarily suffered by military personnel in wartime, it has since been understood as a disorder arising from diverse types of traumas, including natural disaster, such as hurricane or tornado; child physical and sexual abuse; domestic violence; life-threatening illness; accidents; and terrorist attacks. Most people (81.7%) experience one or more traumas in their lifetime, per the National Comorbidity Survey Replication (Sledjeski, Speisman, & Dierker, 2008). Yet, remarkably, most people who experience trauma do not go on to develop PTSD. For those who do develop PTSD after exposure to trauma, their symptoms cluster into four categories as defined by *DSM-5* (APA, 2013): (a) *intrusion symptoms* (e.g., intrusive memories, nightmares, flashbacks); (b) *avoidance symptoms* (e.g., not wanting to talk about the trauma, avoidance of reminders of the trauma); (c) *negative alterations in cognitions and mood* (e.g., distorted self-blame, estrangement from others, diminished interest in activities), and (d) *alterations in arousal and reactivity* (e.g., sleep problems, anger, exaggerated startle response). Additionally, the *dissociative* subtype of PTSD identifies symptoms such as feeling detached from one's mind or body and experiences in which the world seems unreal, dreamlike, or distorted. Persistence of symptoms for over a month and marked decline in functioning are also required. *DSM-5* PTSD differs from *DSM-IV-R* PTSD primarily in the following ways: (a) the definition of "trauma" now includes the phrase "or sexual violence," and there is no longer a requirement for "intense fear, helplessness, or horror" and (b) a new symptom cluster has

been added: "negative thoughts and mood." The 12-month prevalence rate of PTSD in the U.S. population is estimated at 3.5% and lifetime prevalence at 6.8% (Kessler et al., 2005a, 2005b). Global data suggest that similar rates of PTSD are also observed in countries outside of the United States (Kessler et al., 2009).

Most people with PTSD have one or more co-occurring psychiatric diagnoses, including disorders of mood, substance use, anxiety, and personality (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Subjectively, the experience of PTSD is described as a devastating loss that "shatters assumptions" about oneself, others, the future, and the world (Janoff-Bulman, 1992) and that affects perceptions of safety, trust, power, esteem, and intimacy (McCann & Pearlman, 1990). A broad literature on PTSD exists within the professional field and also in literature (e.g., Frankl, 1963; Morrison, 1987; Wiesel, 1960) and film (e.g., *Once Were Warriors*, *Monster*, *This Boy's Life*, *Schindler's List*, *Saving Private Ryan*, *Precious*).

Historically, description of trauma arose in relation to combat, from ancient literature (the *Iliad*) through later history, with terms such as *soldier's heart* during the American Civil War, *shell shock* during World War I, and other terms such as *combat neurosis* and *war hysteria* (Weisaeth, 2002). In 1895, Freud and Breuer proposed that trauma could lead to mental disorder, an idea radical for its time (Wilson, 1994). After the Vietnam War, PTSD was formally named in the *DSM-III* (APA, 1980). The decades since then have seen enormous growth in the study of PTSD, including its epidemiology, assessment, and neurobiological substrates and the development and testing of new treatments for it.

This chapter is designed to be helpful to both clinicians and researchers. It is organized into four sections: key principles, description and empirical validation of PTSD treatments, summary of key findings, and future directions. Due to space limitations and the plentiful array of PTSD models that have arisen in recent years, we have limited this review to models with one or more type 1 studies (randomized controlled trials [RCTs]) published in the peer-reviewed literature from 2010 to February 2014, as well as retaining key type 1 studies from the earlier edition of this chapter (Najavits, 2007). This review is comprehensive in that we included all interventions and studies that met these parameters, plus the following inclusion criteria:

- *Treatments designed for PTSD* (not treatments developed for other diagnoses and applied to PTSD without adaptation)
- *Treatments intended for full PTSD* rather than a specific PTSD symptom (thus excluding Imagery Rehearsal Therapy for nightmares, for example; Casement & Swanson, 2012)
- *Behavioral therapies* (thus excluding medication trials, medication-enhanced psychotherapy, or comparisons of medication vs. psychotherapy)
- *Samples with current PTSD*. We excluded models that only had studies of clients with a history of trauma; subthreshold PTSD; or no PTSD, such as prevention studies.
- *Individual or group treatment modality*. We excluded couple and family treatments as these are less frequently practiced.
- *Adult PTSD treatments*. We cover adolescent studies if they were in addition to at least one adult RCT. For treatments specifically designed for children or children and their caregivers, the interested reader is directed to www.nctsn.org and www.nrepp.org. Examples of such treatments are Child-Parent Psychotherapy (Lieberman, Van Horn, & Ippen, 2005) and Trauma-Focused CBT (Cohen, Mannarino, & Iyengar, 2011).
- *Studies that report pretreatment to end-of-treatment PTSD outcomes*. Studies that do not provide end-of-treatment outcomes have been excluded (e.g., McGovern, Lambert-Harris, Alterman, Xie, & Meier, 2011).

In terms of our reporting, we focus solely on PTSD outcomes unless the treatment was designed to address a comorbid condition (e.g., substance use disorder [SUD]), in which case we also report on that. We do not address secondary outcomes, nor treatment dismantling results. We focus on intent-to-treat analysis, not subgroup analyses, unless intent-to-treat was not available. We also focus on differences between treatment conditions, as all studies were RCTs. We do not address follow-up periods after the end of treatment, as our goal is to prioritize the internal validity of treatment effects. References to more detailed descriptions and research reviews are provided throughout for readers who desire additional information. All models are listed in alphabetical order within sections.

KEY PRINCIPLES

Across the available literature, we note several overarching principles:

1. *PTSD treatments work, and work better than treatment as usual (TAU).* Research shows consistent evidence that treatments designed for PTSD do indeed work. This is the conclusion drawn by every major review and meta-analysis on psychosocial treatments for PTSD (e.g., Bisson, Roberts, Andrew, Cooper, & Lewis, 2013; Bradley, Greene, Russ, Dutra, & Westen, 2005; Butler, Chapman, Forman, & Beck, 2006; Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010; Watts et al., 2013) and professional practice guidelines such as the International Society for Traumatic Stress Studies (Foa, Keane, Friedman, & Cohen, 2008), the Royal College of Psychiatrists and the British Psychological Society (2005), Veterans Health Administration (2004), Institute of Medicine (2008), and the Agency for Healthcare Research and Quality (Jonas et al., 2013).

   The degree of improvement is in the moderate to high range. For example, according to a meta-analysis by Bradley and colleagues (2005), 67% of clients who complete PTSD treatment no longer meet criteria for the disorder ("completer analysis"), and 56% of clients who enroll in PTSD treatment no longer meet criteria for the disorder ("intent-to-treat analysis"). Effect sizes, which reflect degree of change, are reported to average 1.43 from pretreatment to end of treatment, 1.11 when comparing PTSD treatment versus waitlist control conditions, and 0.83 when comparing PTSD treatment versus supportive therapy control condition. Consistent with these findings, another recent meta-analysis reported an average effect size of 1.14 across PTSD psychotherapy studies (Watts et al., 2013).

   Despite the overall positive outcomes for PTSD treatments, it is important to recognize several major caveats that generally receive less scrutiny. Dropout rates are a concern PTSD treatments are usually conducted in individual modality by highly trained clinicians, which add up to relatively costly treatments; and a substantial proportion of study participants had prior PTSD treatment and/or other relevant treatments during the course of studies, including medications (thus calling into question the impact of any particular episode of PTSD behavioral therapy; Najavits, 2013).
2. *The PTSD literature has achieved strong results in part by excluding more severe and complex clients.* The PTSD literature has historically and consistently excluded clients with complexities such as the following (Bradley et al., 2005; Najavits & Hien, 2013; Ronconi, Shiner, & Watts, 2014):
   - Homelessness
   - SUD (especially alcohol or drug dependence and drug use disorders generally)
   - Domestic violence
   - Suicidal or homicidal ideation
   - Serious and persistent mental illness
   - Significant medical illnesses such as HIV
   - Mandated treatment
   - Pregnancy
   - Cognitive impairment
   - Current incarceration

   Thus, the PTSD literature needs to be understood in light of such major limitations. Less positive treatment outcomes are likely when a broader range of clients are included. For example, a treatment often labeled as "gold standard" for PTSD, Prolonged Exposure, has more positive results when studied in PTSD-alone than PTSD/SUD samples (Najavits, 2012, 2013). Notably, treatment models designed for comorbid PTSD/SUD tend to have fewer exclusions in their study samples.
3. *Various treatments are effective, thus allowing clinicians and clients to choose based on their preferences.* A major advance has been the growing evidence base of many PTSD models. Thus, there is no one right way but many. It is possible to select effective treatments based on the clinician's training, the treatment context, and clients' presentation and preferences.
4. *PTSD treatments fall into two broad categories: past-focused and present-focused (or their combination).* Past-focused PTSD models ask the client to explore the trauma narrative in detail to promote "working through" or processing of painful memories and emotions of the trauma. In contrast, present-focused PTSD models focus on psychoeducation and

coping skills to improve current functioning in domains such as interpersonal, cognitive, and behavioral skills. Examples of past-focused models include Cognitive Processing Therapy (CPT), Eye Movement Desensitization and Reprocessing (EMDR), Narrative Exposure Therapy, and Prolonged Exposure. Examples of present-focused models include Cognitive Therapy for PTSD (CT-PTSD), Seeking Safety, and Stress Inoculation Training.[1]

5. *Overall, effective treatments do not differ significantly from each other.* For example, present- and past-focused models both work, and neither consistently outperforms the other (Bisson et al., 2013; Jonas et al., 2013). This is often a surprise to clinicians and clients, who typically assume that telling the trauma narrative is "more powerful" or "necessary" for healing. Similarly, within any category, treatments do not differ significantly from one another. For example, among past-focused treatments, EMDR and Prolonged Exposure both work, and neither outperforms the other (Benish, Imel, & Wampold, 2008; Bisson et al., 2013; Bradley et al., 2005; Powers et al., 2010; Watts et al., 2013).
6. *Combining effective treatments is intuitively appealing, but research so far suggests it is not needed.* Various studies have compared combinations of effective treatments (e.g., Prolonged Exposure plus Stress Inoculation Training or Cognitive Therapy), but the combined treatment consistently shows no greater efficacy than the single treatments being studied (Bryant et al., 2008; Bryant, Moulds, Guthrie, Dang, & Nixon, 2003; Foa et al., 1999, 2005; Foa, Rothbaum, Riggs, & Murdock, 1991; Glynn et al., 1999; Moser, Cahill, & Foa, 2010).
7. *The empirical base has improved greatly over the past decade.* The field now has more studies, more models, and a wider range of populations (e.g., comorbid clients, adolescents); the use of technology such as virtual reality and telehealth; and improved study methodologies.
8. *In addition to evidence-based treatments, the PTSD field has various untested treatments.* Some treatments have never been tested; others have been evaluated only in case studies or uncontrolled pilots. Such treatments may hold promise, and thus it is important to remember that "absence of evidence is not evidence of absence."
9. *Additional research is needed.* Important topics include how to improve training and dissemination of evidence-based treatments; larger sample sizes; broader populations to include more complex and severe clients; exploration of interactions between client and clinician variables in relation to treatment models; longer follow-ups; effectiveness studies; optimal timing of treatments; greater attention to external uncontrolled treatments; improvement in access to care; and further study of promising models.

DESCRIPTION AND EMPIRICAL VALIDATION OF TREATMENTS

In this section, we describe specific PTSD therapies and their RCT evidence. Models are identified as *past-* and/or *present-focused* per point 4 above. Past-focused models are reviewed first due to the larger quantity of literature on these models.

Past-Focused Treatments

The past-focused treatments listed in this section (Table 18.1) share a common strategy of asking the client to explore the past in detail. The models differ in some aspects of their approaches, including how explicitly the trauma narrative is expressed, whether nonverbal modalities are used (e.g., physical sensations), and whether other techniques are incorporated. But overall, these models have as their central goal a deep therapeutic exploration of past trauma. As such, they typically evoke intense emotions, such as rage, sadness, panic, and fear. The client is encouraged to face trauma memories and emotions fully, after which she or he is guided to return to the present by the end of the session.

In some models, the clinician guides the client to focus on "hot spots" that may be especially painful (such as the look on the face of a dying child or the smell of smoke from a fire). To increase the vividness of memories, the client may be asked to notice all senses (smell, sight, sound, touch, hearing) and speak in the present tense. The client may be asked to repeat the trauma narrative many times until it no longer holds strong emotional power. The client essentially *works through* or *processes* the trauma. If the client experienced multiple traumas, she or he

TABLE 18.1 Selection[a] of Past-Focused Posttraumatic Stress Disorder (PTSD) Treatment Models with Type 1 Randomized Controlled Trials

Treatment Model	*Modality*	*Population(s)*	*Comparison Condition(s)*
Abreactive Ego State Therapy	Individual	Mixed PTSD sample	Ochberg Counting Method
Accelerated Resolution Therapy	Individual	Mixed PTSD sample	Attention control
Cognitive Processing Therapy	Individual	Incarcerated adolescents, veterans, survivors of child sexual abuse, interpersonal trauma, military sexual trauma, sexual assault	Minimal attention, Prolonged Exposure, Present-Centered Therapy, treatment as usual, waitlist
Emotional Freedom Techniques	Individual	Mixed PTSD sample, veterans	EMDR, standard of care/waitlist
Eye Movement Desensitization and Reprocessing (EMDR)	Individual	Female sexual assault survivors, mixed PTSD sample, health maintenance organization patients, primary care patients, veterans	Biofeedback-assisted relaxation, Brief Eclectic Psychotherapy, Emotional Freedom Techniques, Prolonged Exposure, Prolonged Exposure + cognitive restructuring, relaxation, routine clinical care, waitlist
Narrative Exposure Therapy	Individual	Earthquake survivors, refugees	Psychoeducation, supportive counseling, treatment as usual, waitlist
Prolonged Exposure	Group, individual	Adolescents, female sexual assault survivors, mixed PTSD sample, Japanese civilians, female veterans and active duty military, motor vehicle accident survivors, people living with HIV, primary care patients, survivors of combat and terrorism, veterans	Cognitive Processing Therapy, Cognitive Therapy, EMDR, monitoring group, Present-Centered Group Treatment, Present-Centered Therapy, Prolonged Exposure + cognitive restructuring, relaxation, Stress Inoculation Training, supportive counseling, Time-Limited Dynamic Therapy, treatment as usual, waitlist
Structured Writing Therapy for PTSD	Individual	Comorbid PTSD/substance use disorder	Treatment as usual
Virtual Reality Exposure Therapy	Individual	Veterans	Minimal attention
Written Exposure Therapy	Individual	Motor vehicle accident survivors	Waitlist

[a] Per inclusion criteria as defined at the start of the chapter.

may be encouraged to fully process one trauma, usually the most upsetting one, and then move to others.

Among the many versions of such treatments, several have accumulated an evidence base. Such treatments represent a helpful method that may achieve results in relatively short time frames, particularly for single-incident trauma. However, such methods may be contraindicated due to the fact that intense trauma memories and emotions can be too disturbing for clients who are currently unstable, such as those who are in domestic violence relationships, who are homeless, who have SUD, or who have suicidal or homicidal ideation (Najavits, 2002; Solomon & Johnson, 2002). Also, clients may be poor candidates for these models if they lack memory for their trauma, have severe dissociation, or have major cognitive impairment (Coffey, Schumacher, Brimo, & Brady, 2005). Thus, such complex clients have been excluded from the vast majority of PTSD outcome trials, as noted earlier in this chapter.

Abreactive Ego State Therapy

Abreactive Ego State Therapy emphasizes the repeated, hypnotically activated "reliving" of the trauma event, combined with ego-strengthening techniques conducted by a co-clinician (Barabasz, Barabasz, Christensen, French, & Watkins, 2013). In recent studies of a 5- to 6-hour single session of manualized Abreactive Ego State Therapy, it outperformed a placebo comparison (the Ochberg Counting Method) in mixed PTSD samples (Barabasz et al., 2013; Christensen, Barabasz, & Barabasz, 2013).

Accelerated Resolution Therapy

Accelerated Resolution Therapy is a brief treatment developed for adults with comorbid PTSD and depression (Kip et al., 2013). It uses imaginal exposure (the client "imagines" the trauma in detail) in conjunction with the clinician oscillating the hand at the client's eye level, with the client engaging in left-to-right eye movements as a way to reduce physiological sensations related to the recall of a trauma. After this exposure to trauma material, the clinician then facilitates "voluntary image replacement" by asking the client to replace distressing images or senses with positive images. Although Accelerated Resolution Therapy is similar to EMDR (see below), it is distinct in its use of image replacement, its primary focus on processing of physiological sensations, and use of a fixed number of eye movements (Kip et al., 2013). In an RCT with survivors of military trauma, those receiving Accelerated Resolution Therapy evidenced greater reduction in PTSD symptoms than those in an attention control condition (Kip et al., 2013).

Cognitive Processing Therapy

CPT was originally developed for female rape victims (Resick & Schnicke, 1992) but has since been tested in other populations per Table 18.1. The model draws heavily on McCann and Pearlman's 1990 trauma themes of safety, trust, power, esteem, and intimacy (Solomon & Johnson, 2002). There is a strong focus on cognitive restructuring to address overly generalized beliefs ("the world is unsafe") and overly constricted beliefs ("it's all my fault"). The client typically writes a trauma narrative as homework outside of the therapy session.

In RCTs of CPT, it has outperformed minimal attention (Resick, Nishith, Weaver, Astin, & Feuer, 2002), TAU (Forbes et al., 2012), and waitlist control conditions (Ahrens & Rexford, 2002; Chard, 2005; Galovski, Blain, Mott, Elwood, & Houle, 2012; Macdonald, Monson, Doron-Lamarca, Resick, & Palfai, 2011; Monson et al., 2006). CPT has also been directly compared with Prolonged Exposure; both evidenced positive outcomes and there were no differences between them on PTSD outcomes (Resick et al., 2002). When CPT was studied in relation to Person-Centered Therapy, a present-focused model, it outperformed the latter on self-reported but not clinician-assessed PTSD symptoms (Suris, Link-Malcolm, Chard, Ahn, & North, 2013). For a review, see Koucky, Dickstein, and Chard (2013).

Emotional Freedom Techniques

The Emotional Freedom Techniques approach (Craig, 1999) assumes that PTSD is the byproduct of trauma-related disturbances in the body's energy field. The treatment uses light manual stimulation of the endpoints of traditional acupuncture meridians on the face, upper body, and hands, while the client focuses on the trauma. In an RCT with veterans, Emotional Freedom Techniques outperformed a waitlist control (Church et al., 2013). In a study comparing Emotional Freedom Techniques versus EMDR in a mixed PTSD sample, PTSD reductions were found in both conditions; however, more EMDR clients achieved clinically significant PTSD change (Karatzias et al., 2011).

Eye Movement Desensitization and Reprocessing

In EMDR therapy (Shapiro, 1995) the client focuses on trauma while engaging in bilateral (back-and-forth) eye movements by tracking the clinician's raised fingers horizontally across the visual field. The client reports thoughts, emotions, and physical sensations that emerged. Processing involves reducing negative emotions and physical sensations (e.g., chest tension); and strengthening positive beliefs (e.g., "I'm now in control"). Some clinicians use tapping or tones instead of eye movements as the essential element is believed to be dual awareness (Jeffries & Davis,

2013). Detailed descriptions of the trauma, extended exposures, and homework are not used.

Various RCTs of EMDR have been conducted (for reviews and meta-analyses, see, e.g., Bisson et al., 2013; Bradley et al., 2005; Butler et al., 2006; Verstrael, van der Wurff, & Vermetten, 2013; Watts et al., 2013). EMDR has outperformed control conditions such as waitlist (Power et al., 2002; Rothbaum, 1997; Rothbaum, Astin, & Marsteller, 2005) and routine clinical care (Carlson, Chemtob, Rusnak, Hedlund, & Muraoka, 1998; Marcus, Marquis, & Sakai, 1997), although in one study it did not outperform a relaxation control other than on one variable (Taylor et al., 2003). Compared to active treatments, it has outperformed Biofeedback-Assisted Relaxation (Carlson et al., 1998) and has resulted in faster recovery than Brief Eclectic Psychotherapy (Nijdam, Gersons, Reitsma, de Jongh, & Olff, 2012) and more clinically significant change than Emotional Freedom Techniques (Karatzias et al., 2011). It has been most studied in relation to Prolonged Exposure (Power et al., 2002; Rothbaum et al., 2005; Taylor et al., 2003). The overall finding, based on meta-analyses, is that both models work yet do not evidence differences in their outcomes or in duration of treatment (Bisson et al., 2013; Bradley et al., 2005; Powers et al., 2010; Watts et al., 2013).

Narrative Exposure Therapy

Narrative Exposure Therapy was originally developed for survivors of war and torture (Schauer, Neuner, & Elbert, 2005). It does not identify a single trauma event as the focus of therapy; rather, it guides the client to construct a detailed chronological account of his or her history, integrating the trauma narrative into a cohesive life story. In RCTs, Narrative Exposure Therapy has outperformed a waitlist control (Zang, Hunt, & Cox, 2013), TAU (Stenmark, Catani, Neuner, Elbert, & Holen, 2013), and psychoeducation and supportive counseling (Neuner, Schauer, Klaschik, Karunakara, & Elbert, 2004). For a review, see Robjant and Fazel (2010).

Prolonged Exposure

Prolonged Exposure starts with several sessions of preparation of the client, after which the client can engage in both imaginal exposure (the client "imagines" the trauma) and in vivo exposure (the client faces reminders of the trauma, such as touching clothing that was worn at the time of the trauma) (Foa, Hembree, & Rothbaum, 2007). Breathing retraining is also recommended. There is a strong focus on exposure homework, including writing or audiotaping a trauma narrative to review between sessions.

Prolonged Exposure has had various RCTs (for reviews and meta-analyses, see, e.g., Foa, 2011; McLean & Foa, 2011; Powers et al., 2010; Rauch, Eftekhari, & Ruzek, 2012). RCTs comparing Prolonged Exposure to active treatments have reported positive outcomes but no differences between Prolonged Exposure and CPT (Resick et al., 2002); Cognitive Therapy (Marks, Lovell, Noshirvani, Livanou, & Thrasher, 1998; Tarrier et al., 1999); EMDR (Rothbaum et al., 2005); Present-Centered Group Treatment (Schnurr et al., 2003); or Stress Inoculation Training (Foa et al., 1999). In a few RCTs, there have been differences between treatment conditions. For example, Prolonged Exposure has outperformed Relaxation Training (Marks et al., 1998; Taylor et al., 2003) and Time Limited Dynamic Therapy (using a developmentally adapted Prolonged Exposure therapy for adolescents; Gilboa-Schechtman et al., 2010).

Prolonged Exposure has outperformed some minimal control conditions, including a monitoring control condition (Pacella et al., 2012), TAU (Asukai, Saito, Tsuruta, Kishimoto, & Nishikawa, 2010; Nacasch et al., 2011), waitlist control (Foa et al., 2005; Glynn et al., 1999; Power et al., 2002), and supportive counseling (Bryant et al., 2003; Foa, McLean, Capaldi, & Rosenfield, 2013a; Foa et al., 1991). However, a recent RCT for clients with comorbid PTSD and SUD compared Prolonged Exposure to BRENDA (a supportive counseling model) and found that both models improved PTSD and SUD, with no difference between them at the end of treatment in either domain (Foa et al., 2013b).

Virtual Reality Exposure Therapy

Virtual Reality Exposure Therapy is a version of exposure therapy that makes use of advanced graphics, sound effects, and computer technology to immerse the client in a realistic, visually rich virtual environment. For example, one model for military veterans

has the client don headgear to view "a virtual Huey helicopter flying over a virtual Vietnam, and a clearing surrounded by jungle" (Rothbaum, Hodges, Ready, Graap, & Alarcon, 2001). As the client moves, the scene appears to move, too, via body-tracking devices.

Such technology-intensive models have become more common in recent years and are beginning to accumulate evidence that both Virtual Reality Exposure Therapy and traditional exposure therapies have positive outcomes, with no differences between them (for reviews, see Goncalves, Pedrozo, Coutinho, Figueira, & Ventura, 2012; Motraghi, Seim, Meyer, & Morissette, 2014; Rizzo et al., 2011; Rothbaum, Rizzo, & Difede, 2010). A recent study of military personnel found that Virtual Reality Exposure Therapy outperformed a minimal attention control on criterion C symptoms of PTSD (avoidance/numbing) and posttraumatic guilt (Miyahira et al., 2012).

Written Exposure Therapies

Written exposure therapies focus on processing trauma memories through writing. These approaches are derived from the early work of Pennebaker and Beall (1986), who had clients repeatedly write about their most traumatic experience with as much emotion and detail as possible. Such approaches go by a number of names (e.g., Structured Writing Therapy, Written Disclosure, Written Exposure Therapy) and have generally evidenced similar treatment effects as therapies using oral disclosure of the traumas (see Frattaroli, 2006, for a review).

For example, in an RCT of a brief, five-session Written Exposure Therapy with motor vehicle accident survivors, Written Exposure Therapy outperformed waitlist control (Sloan, Marx, Bovin, Feinstein, & Gallagher, 2012). However, a recent study in clients with comorbid PTSD and SUD found that Structured Writing Therapy did not outperform TAU on PTSD or SUD outcomes, with both conditions reducing the symptom severity of both disorders (van Dam, Ehring, Vedel, & Emmelkamp, 2013).

Present-Focused Treatments

Present-focused PTSD treatments (Table 18.2) provide psychoeducation and coping skills training. Various cognitive, behavioral, and interpersonal methods are used, such as grounding (sensory focus to recenter in the present so as to reduce upsetting

TABLE 18.2 Selection[a] of Present-Focused Posttraumatic Stress Disorder (PTSD) Treatment Models with Type 1 Randomized Controlled Trials

Treatment Model	*Modality*	*Population(s)*	*Comparison Condition(s)*
Cognitive Therapy for PTSD (CT-PTSD)	Individual	Children, mixed PTSD sample, motor vehicle accident survivors	Assessment only, emotion-focused supportive therapy, Prolonged Exposure, Prolonged Exposure + cognitive restructuring, relaxation, self-help booklet, Trauma-Focused Cognitive-Behavioral Therapy, waitlist
Seeking Safety	Group, individual	Groups with comorbid PTSD/substance use disorder: adolescent girls, homeless women veterans, incarcerated women, low-income urban women, male veterans, women	Enhanced residential services, Relapse Prevention, standard community care, treatment as usual, waitlist, Women's Health Education
Stress Inoculation Training	Individual	Female sexual assault survivors	Prolonged Exposure, supportive counseling, waitlist
Trauma Affect Regulation: Guide for Education and Therapy (TARGET)	Group, individual	Delinquent adolescent girls, incarcerated women, mothers	Present-Centered Therapy, relational supportive therapy, supportive group therapy, waitlist

[a] Per inclusion criteria as defined at the start of the chapter.

emotions), learning to ask for help, identifying and coping with PTSD triggers, rehearsing compassionate self-statements, getting out of unsafe relationships, developing a schedule of productive activities, and cognitive restructuring.

Cognitive Therapy for Posttraumatic Stress Disorder

In CT-PTSD, the goal is to help clients become aware of their maladaptive beliefs and modify them to become more adaptive. This may include, for example, correcting excessively negative assumptions about the trauma (e.g., self-blame); exploring the connection between beliefs, feelings, and behavior; and identifying inaccurate appraisal of threats in the current environment. Examples of models include those by Ehlers, Clark, Hackmann, McManus, and Fennell (2005), Foy (1992), and Tarrier and colleagues (1999). A cognitive component is also part of many of the past-focused models reviewed above, as well as many of the combination models reviewed below; however, as described here, CT-PTSD does not include a past-focused component.

Several RCTs of CT-PTSD have been conducted; see the review by Butler and colleagues (2006) and a recent meta-analysis by Ougrin (2011). In comparisons with active treatment conditions, CT-PTSD and active treatments generally reduce PTSD symptoms, with no difference between them. Examples include Prolonged Exposure (Marks et al., 1998; Tarrier et al., 1999) and Trauma-Focused Cognitive Behavioral Therapy (Nixon, Sterk, & Pearce, 2012). CT-PTSD has outperformed Relaxation Training (Marks et al., 1998), a self-help booklet (Ehlers et al., 2003), and Emotion-Focused Supportive Therapy (Ehlers et al., 2014). It has also outperformed a number of minimal control conditions, including assessment only (Ehlers et al., 2003) and waitlist (Ehlers et al., 2005, 2014).

Seeking Safety

Seeking Safety was designed to treat comorbid PTSD and SUD (Najavits, 2002). It focuses on the core theme of safety, with 25 topics that address cognitive, behavioral, and interpersonal coping skills to address both disorders at the same time (integrated therapy) from the start of treatment (first-stage therapy). Examples of topics are, for example, *asking for help*, *compassion*, *healing from anger*, *healthy relationships*, *honesty*, and *creating meaning*. It emphasizes flexibility, with skills addressed in any order the clinician chooses, and variable treatment length and pacing.

Various RCTs of Seeking Safety have been conducted. Seeking Safety is the only model thus far for comorbid PTSD and SUD that has outperformed a control condition on SUD (see Najavits & Hien, 2013, for a review). In a study of men veterans, Seeking Safety outperformed TAU on SUD (drug use disorder); PTSD and alcohol use disorder improved in both conditions, with no difference between them (Boden et al., 2012). In a study of community-based women, both Seeking Safety and Relapse Prevention (an active comparison) reduced PTSD and SUD symptoms, with no difference between them, and both treatments outperformed a nonrandomized TAU arm on PTSD and SUD (Hien, Cohen, Miele, Litt, & Capstick, 2004). In a study of adolescent girls, Seeking Safety outperformed TAU on SUD and trauma symptoms but not PTSD (Najavits, Gallop, & Weiss, 2006). In a study of partial-dose Seeking Safety using less than half the model, both Seeking Safety and Women's Health Education (an active comparison) reduced PTSD symptoms, with no difference between them (Hien et al., 2009). SUD did not decrease in either study arm, but close to half the sample was abstinent from substances at baseline. An RCT on PTSD and alcohol use disorder (AUD) compared partial-dose (12 session) Seeking Safety with the antidepressant sertraline versus Seeking Safety with placebo (Hien et al., in press). Both conditions improved in both PTSD and alcohol use severity ; moreover, the Seeking Safety plus sertraline condition had greater PTSD improvements than Seeking Safety plus placebo. This study indicates that Seeking Safety, with or without antidepressant medication, evidenced significant improvements in both disorders, even with just a partial dose.

Stress Inoculation Training

Stress Inoculation Training for PTSD is designed to help clients manage anxiety and cope better. It can include breathing exercises, relaxation, psychoeducation, thought stopping, cognitive restructuring, role playing, and guided self-dialogue (Foa et al., 1991). Compared to Prolonged Exposure, Stress Inoculation Training was superior in one study (Foa et al., 1991) but showed no difference in another (Foa et al.,

1999). Stress Inoculation Training has outperformed supportive counseling and waitlist control (Foa et al., 1991, 1999). We were unable to locate any recent RCTs on Stress Inoculation Training.

Trauma Affect Regulation: Guide for Education and Therapy

Trauma Affect Regulation: Guide for Education and Therapy (TARGET) teaches affect-regulation skills relevant to trauma (Ford & Russo, 2006). Its seven skills are summarized by "FREEDOM": "*F*ocusing the mind on one thought at a time; *R*ecognizing current triggers for emotional reactions; distinguishing dysregulated versus adaptive *E*motions; *E*valuations (thoughts), goal *D*efinitions, and behavioral *O*ptions; and self-statements affirming that taking responsibility for recovering from intense emotions is crucial not only to one's personal well-being but also to *M*aking a positive contribution to primary relationships and the community" (Ford, Steinberg, & Zhang, 2011).

In an RCT comparing TARGET to Present-Centered Therapy there were no differences between them in PTSD diagnosis or clinically significant change in PTSD symptoms, but both treatments outperformed waitlist on these variables (Ford et al., 2011). In an RCT of TARGET versus relational supportive therapy, there was no difference between them except for one variable favoring TARGET (PTSD criterion B [i.e., intrusive reexperiencing symptoms]; Ford, Steinberg, Hawke, Levine, & Zhang, 2012). Similarly, in an RCT comparing TARGET to supportive group therapy, both reduced PTSD symptoms, with no difference between them (Ford, Chang, Levine, & Zhang, 2013).

Combination Treatments (Past-Plus Present-Focused)

In this section, we review models that combine past- and present-focused treatments, an intuitively appealing attempt to create a stronger model of therapy (Table 18.3).

TABLE 18.3 Selection[a] of Combination Past- Plus Present-Focused Posttraumatic Stress Disorder (PTSD) Treatment Models with Type 1 Randomized Controlled Trials

Treatment Model	*Modality*	*Population(s)*	*Comparison Condition(s)*
Abreactive Ego State Therapy	Individual	Mixed PTSD sample	Ochberg Counting Method
Brief Eclectic Psychotherapy	Individual	Mixed PTSD sample, police officers	EMDR, minimal attention, waitlist
Concurrent Treatment of PTSD and SUD Using Prolonged Exposure (COPE)	Individual	Comorbid PTSD/ substance use disorder (SUD)	Treatment as usual
Dialectical Behavior Therapy for PTSD (DBT-PTSD)	Individual and group	Survivors of child sexual abuse	Waitlist
Integrated Cognitive-Behavioral Therapy (CBT) for PTSD and Alcohol Use Disorder	Individual	Comorbid PTSD/ alcohol use disorder	CBT for alcohol use disorder + supportive counseling
Resilience-Oriented Treatment for PTSD	Group	Veterans	Waitlist
Skills Training in Affective and Interpersonal Regulation (STAIR)/Exposure	Individual	Adult female survivors of childhood abuse	Supportive counseling + Prolonged Exposure, STAIR + supportive counseling, minimal attention waitlist
Trauma Management Therapy	Individual and group	Male veterans	Exposure therapy

[a] Per inclusion criteria as defined at the start of the chapter.

Brief Eclectic Psychotherapy

Brief Eclectic Psychotherapy is composed of two primary phases: imaginal exposure and cognitive restructuring (Gersons, Carlier, & Olff, 2004). Its core treatment components are also used in other cognitive-behavioral therapies, including psychoeducation, imaginal exposure, writing assignments, and cognitive restructuring. However, Brief Eclectic Psychotherapy is unique in its use of exposure for catharsis, inclusion of mementos and farewell rituals, and incorporation of psychodynamic elements (Schnyder, Muller, Maercker, & Wittmann, 2011).

Brief Eclectic Psychotherapy has outperformed a minimal attention control (Schnyder et al., 2011) and waitlist (Gersons, Carlier, Lamberts, & van der Kolk, 2000). It has also been directly compared with EMDR, with both evidencing positive outcomes on PTSD reduction and no differences between them (Nijdam et al., 2012).

Concurrent Treatment of Posttraumatic Stress Disorder and Substance Use Disorder Using Prolonged Exposure

Concurrent Treatment of PTSD and SUD using Prolonged Exposure (COPE) integrates existing treatment components for PTSD and SUD, including motivational enhancement and CBT for SUD; psychoeducation about PTSD/SUD; in vivo and imaginal exposure; and cognitive restructuring (Mills et al., 2012). COPE is a modified version of Concurrent Treatment of PTSD and Cocaine Dependence (Back, Dansky, Carroll, Foa, & Brady, 2001). In a recent RCT, both COPE and TAU reduced PTSD and SUD symptoms among clients with comorbid PTSD/SUD at end of treatment, with no difference between them (Mills et al., 2012).

Dialectical Behavior Therapy for Posttraumatic Stress Disorder

Dialectical Behavior Therapy for PTSD (DBT-PTSD) is an adaptation of DBT, an evidence-based treatment for borderline personality disorder that does not target trauma and has shown limited effects on PTSD (Harned et al., 2008). DBT-PTSD was developed to (1) reduce fear of trauma-related primary emotions, such as fear, disgust, and powerlessness, using exposure techniques; (2) question nonjustified secondary emotions, such as guilt, shame, and self-contempt; and (3) radically accept trauma-related facts (Bohus et al., 2013). In a recent RCT of DBT-PTSD for clients with comorbid PTSD and borderline personality in a residential treatment setting, it outperformed a TAU waitlist control on reduction of PTSD symptoms but not on symptoms of borderline personality disorder (Bohus et al., 2013).

Integrated Cognitive Behavioral Therapy for Posttraumatic Stress Disorder and Alcohol Use Disorder

Integrated Cognitive Behavioral Therapy for PTSD and Alcohol Use Disorder (ICBT-PTSD/AUD) combines CBT and motivational enhancement approaches for alcohol use disorder with exposure therapy and cognitive restructuring for PTSD (Sannibale et al., 2013). An RCT compared ICBT-PTSD/AUD to ICBT-AUD plus supportive counseling (but no PTSD component). Both conditions evidenced reductions in PTSD symptom severity and alcohol consumption, with no difference between them at the end of treatment (Sannibale et al., 2013).

Resilience-Oriented Treatment for Posttraumatic Stress Disorder

Kent, Davis, Stark, and Stewart (2011) developed "a resilience-oriented treatment for PTSD" that seeks to foster clients' resources, such as awareness of positive emotions and social connectedness. These resources are drawn on in later sessions, when group members experience PTSD symptoms or engage in trauma exposure. In a study of veterans with PTSD, the resilience-oriented treatment outperformed waitlist control (Kent et al., 2011).

Skills Training in Affect and Interpersonal Regulation/Exposure

Skills Training in Affect and Interpersonal Regulation followed by exposure therapy (STAIR/Exposure) is a phase-based model developed for adult survivors of child abuse (Cloitre, Koenen, Cohen, & Han, 2002). STAIR/Exposure divides sessions evenly between

skills training (adapted from DBT) and exposure (adapted from Prolonged Exposure). The phase-based concept derives from the work of Herman (1992) and others who identified phases of PTSD recovery, in which coping skills are established before engaging in exposure techniques.

In an RCT, STAIR/Exposure has outperformed minimal attention waitlist (Cloitre et al., 2002). Compared to active, phase-based treatments, it has outperformed supportive counseling followed by exposure therapy and performed equivalent to STAIR followed by supportive counseling (rather than exposure) (Cloitre et al., 2010). For additional discussion of STAIR/Exposure, see Landes and colleagues (2013).

Trauma Management Therapy

Trauma Management Therapy was developed for veterans with PTSD (Turner, Beidel, & Frueh, 2005). It is composed of imaginal and in vivo exposure, followed by social and emotional rehabilitation (veteran-specific training in social skills, anger management, and communication). In a recent RCT, both Trauma Management Therapy and an exposure therapy-only condition reduced PTSD symptoms, with no difference between them; however, Trauma Management Therapy outperformed exposure therapy on measures of social engagement and interpersonal functioning (Beidel, Frueh, Uhde, Wong, & Mentrikoski, 2011).

SUMMARY OF KEY FINDINGS

Effective Treatments

Various treatment approaches show positive outcomes in RCTs with TAU, minimal attention, and waitlist controls. Among the treatment approaches reviewed above, all generally outperform control conditions, with the exception of Structured Writing Therapy, which did not outperform TAU (van Dam et al., 2013). However, with regard to active treatment comparisons, effective treatments do not appear to differ significantly from each other. Within any category (i.e., past- or present-focused), results across RCTs do not indicate consistent, significant differences between active treatments. For example, among past-focused treatments, CPT, EMDR, Narrative Exposure Therapy, and Prolonged Exposure all work, with none consistently outperforming any other (Benish et al., 2008; Jonas et al., 2013; Powers et al., 2010).

Comparison of Present- versus Past-Focused Treatments

Available data indicate no demonstrable difference in outcome between present- and past-focused treatments (e.g., Bisson et al., 2013; Bradley et al., 2005; Butler et al., 2006; Marks et al., 1998; Ougrin, 2011; Schnurr et al., 2003; Watts et al., 2013). This may come as a surprise given a longstanding clinical literature suggesting that both may be needed for PTSD recovery (Herman, 1992). Indeed, some clients and clinicians believe that the "real work" in PTSD treatment is past-focused, with present-focused work merely a precursor or adjunct. In fact, both present- and past-focused PTSD models produce positive outcomes, neither outperforms the other, and both are superior, overall, to control conditions such as waitlist and TAU. Thus, client preferences and clinician training should become the ultimate determinant of which model to choose from among the various models. Indeed, a recent meta-analysis of PTSD treatments used a novel approach by addressing *complexity* of the client population as a moderator (Gerger, Munder, & Barth, 2014). Their conclusion was that specific PTSD treatments (which largely have been past-focused) are the preferential treatment only for clients with less complex clinical problems. For clients with greater complexity, both specific and nonspecific treatments (e.g., present-focused models such as relaxation and supportive counseling) are equally recommended.

Combination of Treatment Approaches

Combining effective treatments is intuitively appealing, but research indicates that it is not needed. Various studies have compared combinations of effective treatments (e.g., Prolonged Exposure plus Stress Inoculation Training or Cognitive Therapy), but the combined treatment typically shows no greater efficacy then either treatment alone (Bryant et al., 2003; Foa et al., 1991, 1999, 2005; Glynn et al., 1999;

Moser et al., 2010). For example, several studies have addressed whether Prolonged Exposure is sufficient by itself or whether adding elements of Cognitive Therapy (i.e., cognitive restructuring and/or coping skills training) improves PTSD outcomes. Several RCTs indicate that the addition of Cognitive Therapy did not improve outcomes over and above pure exposure in various samples (Bryant et al., 2003; Foa et al., 2005; Marks et al., 1998; Moser et al., 2010). Similarly, cognitive or skills models without an exposure component show no difference from those with an exposure component (Cloitre et al., 2010; see also the dismantling study by Resick et al., 2008) In sum, both exposure and cognitive therapy components produce positive outcomes but do not appear to enhance treatment effects when combined. One exception is a study that reported better PTSD outcomes for a combination of imaginal exposure, in vivo exposure, and cognitive restructuring compared to exposure alone (Bryant et al., 2008).

Treatments for Comorbid Posttraumatic Stress Disorder and Substance Use Disorder

Recent years have seen an increase in the number of treatment models developed for and tested with clients with comorbid PTSD and SUD. Indeed, SUD is the only disorder comorbid with PTSD that has received notable research attention. Similar to treatment models developed for PTSD, models developed for comorbid PTSD/SUD fall into present-focused, past-focused, or combination categories. Seeking Safety, a present-focused treatment, is the most studied evidence-based model. It is the only model thus far studied for PTSD/SUD that has outperformed a control in RCTs (see Najavits & Hien, 2013, for a review). In contrast, past-focused models, which have been studied in four recent RCTs, indicated no difference from the control on either PTSD or SUD at end of treatment. Neither Structured Writing Therapy (van Dam et al., 2013) nor COPE (Mills et al., 2012) outperformed TAU, and neither Prolonged Exposure nor ICBT-PTSD/AUD outperformed supportive counseling (Foa et al., 2013b; Sannibale et al., 2013). Additional reviews of treatments for comorbid PTSD/SUD are available (e.g., Brady, Back & Coffey, 2004; Najavits & Hien, 2013; Ouimette & Read, 2013; van Dam et al., 2013).

FUTURE DIRECTIONS

Like the proverbial glass that is both half full and half empty, PTSD treatment outcome research can be viewed in terms of its major advances over the past several years, or from the framework of all that still needs to be studied.

Improvement in Methodology

The methodology of studies investigating psychosocial treatments is much improved compared with 30 years ago. Indeed, the meta-analysis by Bradley and colleagues (2005) found that treatment effect size was positively associated with year of publication, indicating that more recent studies showed more robust effects. However, close inspection of research reports shows a level of methodological variability that is sometimes at odds with the simple "bottom-line message" conveyed in the abstracts. For example, many studies employ small sample sizes, are statistically underpowered, and collect limited follow-up data (Bisson et al., 2013). Many studies do not include or report on key issues that would be helpful for understanding their results (e.g., power analyses, end-of-treatment assessments, comorbid disorders). In the current climate, results of PTSD treatment outcome research may determine what treatments and programs are funded or discontinued; thus, adequate methodology has real-world implications for clients, clinicians, and programs.

Two excellent methods for evaluating the quality of clinical trials are provided in the 2010 Consolidated Standards of Reporting Trials statement (Schulz, Altman, & Moher, 2010) and by Moncrief (see Bisson & Andrew, 2005). Insistence on one or both of these consistently by journal editors and funding agencies could have a dramatic and rapid impact.

The Moncrief scale, for example, considers 23 different methodological criteria and assigns scores to them on a 0-to-2 scale, giving a maximum possible total of 46. The criteria included in the scale are objective and include items such as specification of main outcomes a priori, sample size, follow-up duration, power calculation, method of allocation, allocation concealment, clear description of treatment and adjunctive treatment, blinding of subjects, representative sample recruitment, use of diagnostic criteria, exclusion criteria and number of exclusions and refusals, description

of sample demographics, blinding of assessor, assessment of compliance with treatments, details of side effects, record of number and reasons for withdrawal by group, outcome measures described clearly or use of validated instruments, information on comparability and adjustment for differences in analysis, inclusion of withdrawals in analysis, presentation of results with inclusion of data for reanalysis of main outcomes, appropriate statistical analysis, conclusions justified, and declaration of interests (Bisson & Andrew, 2005, p. 4).

In addition to these could be added the need to report the rate of comorbid Axis I and Axis II diagnoses (given that most PTSD clients have one or more co-occurring disorders), clinician effects, adherence rating, clinician selection and training, method for assigning clients to clinicians, use of a treatment manual, analysis of both completer and intent-to-treat samples, and whether clients were paid to attend treatment sessions. It has also been suggested that using waitlist and TAU comparisons may be responsible for the inflation of effect sizes in RCTs of psychotherapy approaches and that, therefore, direct comparisons between effective psychotherapies are needed to avoid such inflation (Watts et al., 2013).

Broadening of Samples

Recent studies use rigorous selection of PTSD clients (rather than simply a history of trauma) and validated diagnostic tools. Also, a broader array of client populations has been studied in terms of sociodemographic characteristics and trauma type. However, continued expansion in sampling is needed. There are still relatively few studies that include complex individuals, with the most common exclusions being comorbid psychosis, SUD, bipolar disorder, and suicidal ideation (Ronconi et al., 2014). It will be essential to include these individuals in future therapy outcome research to improve the generalizability of results to real-world client populations.

Studies of Dissemination

There is a need for more effectiveness studies that evaluate how treatments fare in real-world implementation and a need to better understand issues such as client and clinician preferences for treatment, use of technology for enhancing treatment, and public health challenges such as how clients can access PTSD treatment in their communities. One such public health challenge is the cost of PTSD treatment, and additional research is needed to determine which treatments are simultaneously cost-effective and effective in reducing PTSD symptoms. For example, although studies of Virtual Reality Exposure Therapy are becoming more prevalent in the literature, these therapies are often more expensive and harder to implement than verbal or written exposure therapies. Given findings that Virtual Reality Exposure Therapy does not outperform traditional exposure therapies (Goncalves et al., 2012; Motraghi et al., 2014; Rizzo et al., 2011; Rothbaum et al., 2010), the use of such technologies may not be necessary to produce clinically significant change.

Additionally, the use of telehealth and Internet technologies to improve treatment access is the subject of a number of recent open pilots and pilot RCTs. Initial results suggest that telehealth and Internet delivery of PTSD treatment is safe and effective (Morland, Hynes, Mackintosh, Resick, & Chard, 2011; Possemato, Ouimette, & Knowlton, 2011; Strachan, Gros, Ruggiero, Lejuez, & Acierno, 2012); however, it may not be as effective as in-person treatment (Gros, Yoder, Tuerk, Lozano, & Acierno, 2011). Larger RCTs of telehealth and Internet-delivered treatments are needed before making any further conclusions about the effectiveness of these approaches.

Delivery of Treatments

Another key area is more refined study of how to deliver treatments. This might include how and when they should be combined (e.g., with other psychosocial treatments), how long to deliver them, when to determine that a treatment is not working for particular clients, outcome differences based on modality and/or pacing of treatment, whether particular clinician characteristics are necessary for effective delivery, and greater understanding of what aspects of treatments are essential.

NOTE

1. The term *trauma-focused* is often used to identify past-focused models and *non–trauma-focused* to identify present-focused models. We eschew these terms, however,

as all present-focused PTSD models directly and strongly "focus on trauma." The difference is how they approach it. Past-focused models primarily focus on the past by exploring intense trauma memories and associated feelings, thoughts, and body sensations. Present-focused models omit detailed exploration of the past, typically in the service of helping stabilize the client, and instead focus primarily on coping skills and psychoeducation. We note too that the term "non-trauma-focused treatment" to refer to such present-focused PTSD models is also problematic as it labels them solely by what they are not. It is equivalent to referring to women as "non-men" or children as "non-adults." Present-focused approaches have a rich content of coping skills and psychoeducation that is better captured by a meaningful label (Najavits & Hien, 2013).

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19

Pharmacological Treatment of Posttraumatic Stress Disorder

Julia A. Golier
Andreas C. Michaelides
Maya Genovesi
Emily Chapman
Rachel Yehuda

Although psychotherapy is considered the first line of treatment for posttraumatic stress disorder (PTSD), there have been some advances made in the pharmacological treatment of this disorder as well. Based on numerous controlled clinical trials, antidepressants are still the first-line pharmacological treatment for this disorder. Multiple studies suggest that selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline, and paroxetine) are efficacious in reducing PTSD-specific symptoms and improving global outcome. Emerging evidence also suggests efficacy for the selective serotonin/norepinephrine reuptake inhibitor venlafaxine. Other individual agents found to be efficacious include the tricyclic antidepressant (TCA) imipramine and the monoamine oxidase inhibitor (MAOI) phenelzine. Prazosin is emerging as a beneficial adjunctive agent in treating PTSD-related sleep disturbances and nightmares. Some evidence suggests that atypical antipsychotics may be efficacious against a broad range of symptoms, although their potential for causing metabolic side effects may limit their widespread use. Controlled clinical trials are needed to assess whether anticonvulsants, cortisol-based treatments, sympatholytics, or other novel, nontraditional approaches are efficacious, and how and when pharmacotherapy can supplement or enhance psychotherapy outcomes. However, these studies should occur in the context of discussion regarding the goals of pharmacotherapy in PTSD as well as the subgroups of patients or clinical presentations most likely to require or benefit from the different pharmacological interventions.

INTRODUCTION

The diagnosis of PTSD first appeared in the anxiety disorder section of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association [APA], 1980), with the intention of describing the characteristic and long-lasting symptoms that occur in individuals following exposure to extremely traumatic events. In the most recent edition, *DSM*-5, PTSD has been reclassified as a trauma- and stressor-related disorder. This new category—which also includes acute stress disorder and adjustment disorder—was developed to explain psychological symptoms that occur following

exposure. Classic explanations of anxiety disorders suggest symptoms with no immediate antecedent or reason, but for traumatic disorders the immediate precipitating factor is known. PTSD includes manifestations of fear and anxiety, fluctuations in mood and dissociative states, changes in personality, and, in its most severe form, symptoms phenotypically similar to psychosis. An important question in PTSD pharmacotherapy has been whether to target individual symptoms or to address the syndrome as a whole.

DIAGNOSTIC CRITERIA

The first diagnostic criterion (Criterion A) for PTSD is that a person must have been exposed to a trauma, currently defined as "actual or threatened death, serious injury, or sexual violence" (APA, 2013). *DSM-5* removes the person's subjective response to trauma—specifically experiencing fear, helplessness, or terror—as a subcriterion since this feature does not provide any additional diagnostic accuracy. The symptoms of PTSD are classified into four discrete clusters that constitute diagnostic Criteria B through E. Intrusive symptoms (Criterion B) include (a) having recurrent and unwanted recollections of the event; (b) having distressing dreams of the event; and (c) acting and feeling as if the event were reoccurring (e.g., dissociative flashback). Additionally, (d) psychological and (e) physiological distress following exposure to symbolic representations of the event may also occur. Avoidant symptoms (Criterion C) reflect behaviors indicative of actively trying to avoid (a) internal (e.g., memories) or (b) external (e.g., places) reminders of the trauma. Symptoms of altered mood or cognitions include (a) the inability to recall important aspects of the trauma (e.g., psychogenic amnesia); (b) negative perceptions about oneself, others, or the world; (c) distorted cognitions regarding the cause or result of the event, leading to blame of others or oneself; (d) a negative emotional state that persists; (e) markedly diminished interest in normally significant activities; (f) feelings of detachment or estrangement from others; and (g) restricted range of affect. Altered arousal and reactivity symptoms include (a) irritability or angry outbursts; (b) a pattern of destructive behavior; (c) hypervigilance; (d) an exaggerated startle response; (e) difficulties with concentration; and (f) sleep problems. Meeting diagnostic criteria for PTSD requires the concurrent presence of at least one intrusive symptom, one avoidant symptom, two altered mood and cognition symptoms, and two altered arousal and reactivity symptoms.

In addition to the above criteria, symptoms must be present for at least 1 month (Criterion F); must be accompanied by clinically significant impairment in social, occupational, or other areas of functioning (Criterion G); and are not attributed to the effects of substances or other medical conditions (Criterion H). If symptoms last for more than 3 months following the traumatic event, the diagnosis of chronic PTSD is given. The diagnosis of delayed-onset PTSD is given if symptoms begin at least 6 months after the traumatic event. PTSD may be diagnosed in any person who meets the above diagnostic criteria, regardless of other preexisting or concurrent psychopathology. To date, the bulk of the existing psychopharmacological literature has been based on the *DSM-IV* criteria, which conceptualized PTSD as being composed primarily of intrusive (Criterion B), avoidant (Criterion C), and hyperarousal (Criterion D) symptom clusters, thus omitting altered cognitions from diagnostic classification.

PREVALENCE

Epidemiological studies have demonstrated that PTSD is a common psychiatric condition, and while there is a significant range in estimations, its lifetime prevalence has been estimated to be as high as 14% in the U.S. general population (Breslau Davis, Andreski, & Peterson, 1991; J. R. Davidson, Hughes, Blazer, & George, 1991; Helzer, Robin, & McEvoy, 1987; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Shore, Vollmer, & Tatum, 1989). Among U.S. military veterans, the point prevalence of PTSD has been estimated to be between 2% and 17% and the lifetime prevalence 6% to 31%. More than 80% of adults in the United States have experienced a traumatic event; estimates of the prevalence of PTSD among those exposed to Criterion A stressors range from 3% to 58% (APA, 1994). This wide range reflects the fact that some types of traumatic events are more likely to result in PTSD than others. Among those who have experienced torture, such as concentration camp survivors and prisoners of war, the prevalence of PTSD can be quite high, with estimates of 50% to 75% in such samples (Goldstein, van Kammen, Shelly, Miller, & Kammen, 1987; Kluznick, Speed, Van Valenburg, &

Magraw, 1986). Among rape victims, approximately one third develop PTSD, and rape accounts for the greatest overlap among genders in the development of the disorder. However, in individuals who have been exposed to natural disasters such as earthquakes, volcanic eruptions, and bushfires, the prevalence of lifetime PTSD is lower, with estimates ranging from 3.5% to 16% (McFarlane, 1992; Shore, Tatum, & Vollmer, 1986; Shore et al., 1989). Estimates of the prevalence of PTSD in trauma survivors may also vary depending on the amount of time that has elapsed between the traumatic event and assessment of PTSD. The few studies examining the longitudinal course of PTSD prospectively demonstrated that frequency of PTSD following a specific traumatic event declines with time (Kessler et al., 1995; McFarlane, 1989; Rothbaum et al., 1992), with symptoms for the majority of trauma survivors resolving within 2 to 3 years. However, for the minority of individuals who remain symptomatic, the symptoms of PTSD may intensify over time, as does the risk of developing secondary and chronic comorbid mood or anxiety disorder, substance abuse, and memory impairment (Freedy, Shaw, & Jarrell, 1992; Golier et al., 2002; Green, Lindy, Grace, & Leonard, 1992; Kulka et al., 1990; North, Smith, & Spitznagel, 1994).

BURDEN OF POSTTRAUMATIC STRESS DISORDER

Exposure to traumatic events and the subsequent development of PTSD can result in significant psychological, physical health, and social consequences for the individual, as well as place a considerable burden on the health care system.

PTSD is associated with a number of adverse mental health outcomes, including other psychopathology, substance use, and self-harm. For example, individuals who experience childhood trauma are at increased risk for suicide (Felitti et al., 1998). Those diagnosed with PTSD are 2 times more likely to develop a depressive disorder and 10 times more likely to develop a panic disorder compared to their counterparts without a diagnosis (Perkonigg, Kessler, Storz, & Wittchen, 2000). Among veterans, there is a greater likelihood to be diagnosed with depression and anxiety in addition to PTSD as compared to PTSD alone, PTSD with anxiety, and PTSD with depression (Ginzburg, Ein-Dor, & Solomon, 2010). Severity of PTSD symptoms is associated with an increase in illicit drug and alcohol use (Ouimette et al., 2008). Kessler, Sonnega, Bromet, Hughes, and Nelson (1995) further estimated the likelihood of being diagnosed with another mental health disorder for both men and women in the general population. Men diagnosed with PTSD are 2 times more likely to be diagnosed with alcohol abuse and dependence, are almost 7 times more likely to be diagnosed with major depressive disorder, are approximately 10 times more likely to be diagnosed with mania, and are approximately 14 times more likely to be diagnosed with three or more psychiatric disorders than their male counterparts without PTSD. In contrast, women diagnosed with PTSD are approximately two times more likely to be diagnosed with alcohol abuse and dependence, are approximately four times more likely to develop major depressive disorder or mania, and are almost eight times more likely to be diagnosed with three or more psychiatric disorders than their female counterparts without PTSD (Kessler et al., 1995). With such cross-sectional analyses it is not always possible to determine whether such diagnoses are distinct comorbid conditions as they may be preexisting vulnerabilities to PTSD or PTSD symptoms themselves. The inclusion of "persistent negative emotional state" as a diagnostic criterion may minimize some of this comorbidity.

There is also significant medical comorbidity with PTSD. Overall, PTSD is associated with an increase in physical symptoms, higher rates of health care utilization, and early-age heart disease mortality (Boscarino, 2008; Deykin et al., 2001). Individuals who experienced four or more instances of childhood trauma demonstrate a 1.5-fold increase in physical inactivity and obesity when compared to individuals without instances of childhood trauma (Felitti et al., 1998). Those diagnosed with PTSD are more likely to develop arthritis, back and neck pain, chronic pain, heart disease, ulcers, and headaches (Sledjeski, Speisman, & Diefker, 2008). These detrimental health trends apply to both veteran and nonveteran populations. Vietnam veterans with PTSD are at greater risk of developing both cardiovascular and autoimmune diseases, including hypothyroidism, rheumatoid arthritis, and psoriasis (Boscarino, 2004). Iraq war veterans with PTSD, compared to those without, report lower ratings of general health, have a greater number of missed work days, and report a higher severity of somatic symptoms (Hoge et al., 2007).

The effects of PTSD can adversely permeate relationships and family life, among other social impacts. Among veterans, 70% of those who carry a PTSD diagnosis report intimate relationship distress, compared to 30% without a PTSD diagnosis (Riggs, Byrne, Weathers, & Litz, 1998). Some estimate that veterans with PTSD are a little more than 5 times more likely to perpetrate an act of domestic violence (e.g., hitting) and 26 times more likely to commit a severe act of violence (e.g., choking) compared to veterans with relationship problems but without a PTSD diagnosis (Sherman, Sautter, Jackson, Lyons, & Han, 2006). Among veterans separated from their partners, 53.7% report that they had conflicts (e.g., shoving) with their partner and 27.6% of veterans reported that their partner was currently afraid of them (Sayers, Farrow, Ross, & Oslin, 2009).

Individuals with PTSD and traumatic experiences are also significantly more likely to engage in risk-taking behaviors (Felitti et al., 1998; Killgore et al., 2008). Those who experience four or more traumatic childhood events are more likely to have a high number of sexual intercourse partners (defined as 50 or more) over their lifetime, which increases their risk of contracting a sexually transmitted infection (Felitti et al., 1998). Additionally, Killgore and colleagues (2008) surveyed 2,244 veterans just returning home from Iraq and found that those who had greater exposure to intense human trauma, had killed someone, or had been exposed to violent combat endorsed a higher tendency to engage in risky behaviors like fast driving and consuming higher quantities of alcohol, and more often expressed aggression toward others.

The increased incidence of comorbid psychopathology and medical problems, risk-taking behaviors, and disruption to family systems among individuals with PTSD places a great burden on the mental health care system. Veterans with PTSD utilize four times more general outpatient mental health services than veterans without PTSD, in addition to PTSD specialty treatment (Possemato, Wade, Andersen, & Quimette, 2010). For global analyses the World Health Organization (WHO) uses the disability adjusted life-years (DALYs) metric to estimate the burden of a disease or disorder. Each DALY represents a healthy year lost across the globe as the result of a disease and is calculated based on specific morbidity and mortality rates. The WHO (2001) estimates that PTSD's global burden of disease is 3,230,000 DALYs, which is similar to that of oral cancer, bladder cancer, and kidney cancer (Murray et al., 2012). Moreover, estimates for PTSD-related costs for returning veterans in the first 2 years are $5,904 to $10,298 on a per-case basis (Tanielian et al., 2008). Kessler and Greenberg (2002) estimate that the total annual cost of anxiety disorders, which include PTSD, is more than $100 billion annually in the U.S. population when taking into account the impact of unemployment, underemployment, and comorbidity costs.

ETIOLOGY

By definition, exposure to a traumatic event is a requirement for the development of PTSD. However, only a minority of persons exposed to even the most severe traumas develop PTSD or another psychiatric illness. In fact, other psychiatric disorders, including substance use and mood disorders, are more strongly associated with exposure to a traumatic event (Perkonigg, Kessler, Storz, & Wittchen, 2000). Therefore, it is important to consider other risk factors that influence the development or persistence of posttraumatic stress symptoms following trauma exposure. These include the severity of the trauma (Foy, Sipprelle, Rueger, & Carroll, 1984; March, 1993; Yehuda, Southwick, & Giller, 1992); past history of stress, abuse, or trauma (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993; Zaidi & Foy, 1994); history of behavioral or psychological problems (Helzer et al., 1987); premorbid psychopathology; genetic factors (True et al., 1993); family history of psychopathology (J. Davidson, Swartz, Storck, Krishnan, & Hammett, 1985); and lower IQ (Macklin et al., 1998) as well as subsequent exposure to reactivating environmental events (Goldstein et al., 1987; Kluznick et al., 1986; McFarlane, 1990; Schnurr, Friedman, & Rosenberg, 1993; Solomon & Preager, 1992; True et al., 1993; Yehuda et al., 1995). Women are also at increased risk for developing PTSD, likely as a result of a greater exposure to assault (Breslau 2002). An awareness of the risk factors can have significant implications for the treatment of this chronic, heterogeneous, and multifaceted disorder, since the associated psychopathology may not only be a direct response to a precipitating traumatic event.

PHARMACOTHERAPY IN ADULTS WITH POSTTRAUMATIC STRESS DISORDER

Rationale for the Use of Pharmacotherapy in Posttraumatic Stress Disorder

An early view of the role of pharmacotherapy in the treatment of PTSD suggested that medications should be considered primarily as adjunctive to psychotherapy by modulating anxiety and depression to facilitate therapy. Antidepressants and anxiolytics were also considered to be indicated owing to the high rates of comorbid mood and anxiety disorders in PTSD. However, as research into the biological underpinnings of PTSD progressed, it became evident that there are alterations in the catecholaminergic and serotonergic systems and in the hypothalamic-pituitary-adrenal (HPA) axis in PTSD and that these were distinct from the alterations seen in other psychiatric disorders (e.g., Charney, Deutch, Krystal, Southwick, & Davis, 1993; Yehuda, Giller, & Mason, 1993). This provided a further rationale to examine an approach to pharmacotherapy in PTSD that might reduce symptoms by acting on the neurotransmitter systems implicated by these alterations. Increasing appreciation of the prevalence, severity, and chronicity of PTSD and the availability of novel psychotropic agents on the market have also fueled the advances made in the pharmacological treatment of this disorder and supported the notion that medication can be a primary treatment for core symptoms of PTSD (J. R. Davidson, 1992; Friedman, 1988).

Assessment of the Efficacy of Pharmacotherapy in Posttraumatic Stress Disorder

Table 19.1 summarizes the open-label and controlled pharmacological trials in the acute-phase treatment of chronic PTSD. The medications studied include antidepressants, antipsychotics, benzodiazepines, hypnotic agents, anticonvulsants and mood stabilizers, and sympatholytics as well as other medications that are emerging as potential treatments (e.g., cortisol-based treatments).

The medications are listed by category, and for each drug the studies are ranked according to their type (type 1 through type 4). To facilitate comparisons among the studies, the table includes information regarding the sample size and gender distribution, treatment population, the percentage changes in total PTSD symptoms from baseline to treatment end point, and the scales used to measure these changes. Additionally, the rate of treatment response is provided, as well as information regarding whether there were beneficial effects on specific symptoms (intrusive, avoidant, or hyperarousal symptoms, depression, or sleep).

The earliest studies used measures of depression or anxiety as primary outcome measures (e.g., the Hamilton Rating Scale for Depression; Hamilton, 1960) before validated scales for PTSD were available. Others have relied on self-report instruments of PTSD symptoms such as the Impact of Events Scale (Horowitz, Wilner, & Alvarez, 1979) and the Mississippi Scale for PTSD (Keane, Caddell, & Taylor, 1988). Over time, studies have increasingly relied on validated clinician-rated instruments such as the Clinician Administered PTSD Scale (CAPS; Blake Weathers et al., 1990), the Treatment of PTSD scale (TOP-8; J. R. Davidson & Colket, 1997), and the Structured Interview for PTSD (SIP; J. R. Davidson, Malik, & Travers, 1997). For more global measures of outcome, the Clinical Global Impression-severity (CGI-S) and Clinical Global Impression-improvement (CGI-I) scales (Guy, 1976) are used. Responder status in PTSD studies is often defined as subjects having been "much improved" or "very much improved" on the CGI. Other definitions are based on categorical levels of symptom improvement—most often defined as a 30% reduction in PTSD symptom severity—which are used alone or in combination with the CGI-I score. Less often, remission rates are reported, defined as the patient no longer meets criteria for the diagnosis or has a CAPS score of 20 or lower, which is indicative of only mild symptoms.

Table 19.1 summarizes acute-phase treatment of PTSD, referring to the initiation of a course of treatment. It does not refer to acute PTSD; for the majority of studies, the illness had been present for years to decades prior to the treatment trial, which often was not the first treatment trial. Details of the duration of illness, time since trauma exposure, and extent of treatment history could not be provided for each study but are mentioned for some of the most influential studies or when such information was particularly germane (e.g., studies of PTSD resistant to SSRIs). The extent of psychiatric comorbidity is also not explicitly summarized in the table, but most studies had high rates of comorbid disorders. Major depression was

TABLE 19.1 Pharmacological Treatment Trials in Chronic Posttraumatic Stress Disorder

Drug Type	*Study Type*	*First Author*	*Drug*	*Duration*	*Subjects*	*Mean Age (yrs)*
MAOIs	1	Baker (1995)	Brofaromine	12 weeks	118 (88.7% men)	45
	1	Kosten (1991)	Phenelzine	8 weeks	37 (100% men)	39
	2	Shestatzky (1988)	Phenelzine	4 weeks	13 (not specified)	39
	3	Lerer (1987)	Phenelzine	4 weeks	22 (100% men)	28
	2	Onder (2006)	Moclobemide	12 weeks	103 (50% men)	31
	3	Neal (1997)	Moclobemide	12 weeks	20 (85% men)	31
Tricyclic or tetracyclic	1	Davidson (1990)	Amitriptyline	8 weeks	40 (100% men)	NR
	3	Çelik (2011)	Amitriptyline	12 weeks	50 (100% men)	
	1	Kosten (1991)	Imipramine	8 weeks	41 (100% men)	39
	2	Reist (1989)	Desipramine	4 weeks	18 (100% men)	NR
	2	Davidson (2003)	Mirtazapine	8 weeks	29 (81% women)	48
	3	Chung (2004)	Mirtazapine	6 weeks	51 (100% men)	59
	3	Kim (2005)	Mirtazapine		12 (75% men)	34
	3	Bahk (2002)	Mirtazapine	24 weeks	15 (66.7% men)	36
	3	Connor (1999)	Mirtazapine	8 weeks	6 (88.4% women)	41
SSRI	1	Connor (1999)	Fluoxetine	12 weeks	53 (93% women)	36
	1	Martenyi (2002b)	Fluoxetine	12 weeks	301 (81% men)	38
	1	van der Kolk (1994)	Fluoxetine	5 weeks	64 (66% men)	41
SSRI	1	Martenyi (2007)	Fluoxetine	12 weeks	411 (71.5% women)	40.7
	1	Martenyi (2006)	Fluoxetine	12 weeks	114 (99% men)	36.2
	2	Onder (2006)	Fluoxetine	12 weeks	103 (50% men)	31
	2	Hertzberg (2000)	Fluoxetine	12 weeks	12 (100% men)	46

Population	*PTSD SX*	*% Improvement Total PTSD Sx*		*Response Rates*		*Efficacy on Subscales and Comorbid Symptoms*				
	Scale	Drug	PBO	Drug	PBO	Int.	Avoid.	Hyp.	Dep.	Sleep
mixed trauma, primarily combat-related	CAPS	33.20%	30.90%	33.00%	31.00%	no	no	no	NR	NR
combat veterans	IES	44.40%	5.1%	68.00%	28.0%	yes	yes	NR	no	NR
mixed trauma, primarily combat-related	PTSD	5.00%	6.20%	NR	NR	no	no	no	no	NR
combat veterans	DSM-111	14.70%		18.20%		yes	no	yes	no	Yes
civilians with trauma after earthquake	CAPS	51.7%	NR	1	NR	yes	yes	yes	NR	NR
civilians and veterans, mixed trauma, primarily motor vehicle accidents	IES	48.6%		61.00%		yes	yes	NR	yes	yes
combat veterans	SIP	32.10%	20.40%	50.00%	16.6%	no	yes	NR	yes	NR
combat veterans	CAPS	10.3% (paroxetine)	20.2% (amitriptyline)	31.8% (paroxetine)	55% (amitriptyline)	yes	no	yes	no	no
combat veterans	IES	24.90%	5.1%	65.00%	28.0%	yes	no	NR	no	NR
combat veterans	IES	2.50%	0.90%	NR	NR	no	no	NR	yes	NR
civilians and veterans, mixed trauma	SIP	42.80%	22.00%	64.70%	20.0%	NR	NR	NR	no	NR
combat veterans	CAPS	43.4%		96.00%		yes	yes	yes	yes	NR
Korean veterans	SIP	52.8%		NR		NR	NR	NR	yes	NR
NR	SIP	46.2%		NR		NR	NR	NR	yes	NR
mixed civilian trauma, primarily vehicle accidents	SIP	37.1%		33.00%		NR	NR	NR	NR	NR
mixed civilian trauma, primarily sexual abuse	DUKE	79.70%	34.4%	85.00%	62.0%‡	NR	NR	NR	NR	NR
mixed trauma, 48% combat exposure	CAPS	43.00%	20.7%	59.90%	43.8%	yes	no	yes	yes	NR
mixed trauma, primarily combat or assault	CAPS			NR		no	yes	yes	yes	NR
mixed trauma, primarily sexual assault	TOP-8	23.1 (20 mg); 27.9 (40 mg)	25.70%	40.5% (20 mg); 38.8% 40 mg)	47.50%	no	no	no	NR	NR
combat veterans	TOP-8	39.5%	20.60%	44%	3.00%	yes	yes	yes	NR	NR
civilians with trauma after earthquake	CAPS	49.6%	NR	1	NR	yes	yes	yes	NR	NR
combat veterans	SIP	2.10%	2.30%	17.00%	33.30%	no	no	no	NR	NR

(*continued*)

TABLE 19.1 (continued)

Drug Type	*Study Type*	*First Author*	*Drug*	*Duration*	*Subjects*	*Mean Age (yrs)*
	3	Nagy (1993)	Fluoxetine	10 weeks	27 (100% men)	45
	3	McDougle (1991)	Fluoxetine	10 weeks	20 (100% men)	41
	3	Burdon (1991)	Fluoxetine	4+ weeks	150 (100% men)	NR
	1	Davidson (2001)	Sertraline	12 weeks	208 (78% women)	38
	1	Zohar (2002)	Sertraline	12 weeks	42 (95% men)	41
	1	Brady (1995)	Sertraline	10 weeks	9 (67% men)	35
	1	Robb (2010)	Sertraline	10 weeks	131 (59.7% female)	10.8
	1	Pananhi (2011)	Sertraline	10 weeks	70 (100% men)	45
	3	Brady (2000)	Sertraline	12 months	187 (73% women)	40
	1	Walderhaug (2010)	Duloxetine	8 weeks	20 (100% men)	52.6
	1	Marshall (2001)	Paroxetine	12 weeks	563 (~66% women)	42
	1	Tucker (2001)	Paroxetine	12 weeks	323 (65.8% women)	42
	1	Schneier (2012)	Paroxetine	10 weeks	37 (54% women)	50
	3	Çelik (2011)	Paroxetine	12 weeks	50 (100% men)	
SSRI	1	Marshall et al. (2007)	Paroxetine	10 weeks	52 (67% women)	39.8
	3	Marshall (1998)	Paroxetine	12 weeks	17 (76% women)	38
	3	Naylor (2013)	Paroxetine	12 weeks	12 (100% men)	35.8
	1	Spivak (2006)	Fluvoxamine	8 weeks	40 (54% men)	42
	3	Davidson (1998)	Fluvoxamine	8 weeks	15 (53% women)	41
	3	Marmar (1996)	Fluvoxamine	10 weeks	11 (100% men)	50

Population	PTSD SX	% Improvement Total PTSD Sx		Response Rates		Efficacy on Subscales and Comorbid Symptoms				
combat veterans	CAPS	34.0%		37.00%		yes	yes	yes	yes	yes
combat veterans		NR		65.00%		NR	NR	NR	NR	NR
veterans		NR		NR		NR	NR	yes	yes	yes
mixed civilian trauma, primarily physical or sexual assault	CAPS	44.60%	36.2%	60.00%	38.0%	no	yes	no	no	no
military veterans, primarily combat	CAPS	20.50%	14.50%	41.00%	20.00%	no	no	no	no	NR
mixed civilian trauma, comorbid alcohol dependence	IES	61.0%		NR		yes	yes	yes	yes	NR
civilian trauma among children and adolescents (6–17)	UCLA PSTD-1	46.50%	54.10%	35%	45%	NR	NR	NR	NR	NR
Iranian Iran–Iraq veterans	IES-R	37.9%	31.30%	19%	9%	yes	yes	yes	NR	NR
mixed civilian trauma, primarily physical or sexual assault	CAPS	43.30%	30.9%	53.00%	32.0%	no	yes	yes	yes	NR
veterans, primarily combat trauma	PTSD-C	24%		42%		no	no	no	yes	no
mixed civilian trauma	CAPS	0.53 (20 mg) 0.51 (40 mg)	34.0%	0.62 (20 mg) 0.54 (40 mg)	37.0%	yes	yes	yes	yes	NR
mixed trauma types, primarily assault, also combat	CAPS	47.80%	33.7%	58.80%	38.0%	yes	yes	yes	NR	NR
civilian trauma related to World Trade Center attack	CAPS	70.0%	45.6%	63.2%	38.9%	NR	NR	NR	no	NR
combat veterans	CAPS	10.3% (paroxetine)	20.2% (amitriptyline)	31.8% (paroxetine)	55% (amitriptyline)	yes	no	yes	no	no
mixed civilian trauma	CAPS	42.1%	25.5%	66.7%	27.3%	yes	yes	no	no	NR
mixed civilian trauma, primarily sexual abuse	IES	48.0%		NR		no	yes	yes	yes	NR
combat veterans	CAPS	17.9%	18.9%	NR	NR	no	no	no	yes	NR
civilian trauma from motor vehicle accident	CAPS; TOP-8	0	NR	NR	NR	yes	yes	yes	yes	NR
mixed civilian trauma, primarily traumatic bereavement and childhood sexual abuse	IES	47.4%		64.20%		yes	yes	yes	NR	NR
combat veterans	IES	42.3%		NR		yes	yes	yes	yes	NR

(*continued*)

TABLE 19.1 (continued)

Drug Type	*Study Type*	*First Author*	*Drug*	*Duration*	*Subjects*	*Mean Age (yrs)*
		Tucker (2000)	Fluvoxamine	10 weeks	17 (76% female)	39
	3	Escalona (2002)	Fluvoxamine	14 weeks	15 (100% men)	47
	3	Neylan (2001)	Fluvoxamine	10 weeks	21 (100% men)	60
	2	Shalev (2012)	Escitalopram	12 weeks	242 (55.8% women)	37.2
	2	Robert (2006)	Escitalopram	12 weeks	25 (100% men)	56
Other antidepressants	1	Davis (2004)	Nefazodone	12 weeks	42 (98% men)	54
	3	Davidson (1998)	Nefazodone	12 weeks	17 (76% women)	46
	3	Davis (2000)	Nefazodone	8 weeks	36 (97% men)	49
	3	Garfield (2001)	Nefazodone	9 weeks	19 (100% men)	50
Other antidepressants	3	Hertzberg (1998)	Nefazodone	12 weeks	10 (100% men)	46
	3	Neylan (2003)	Nefazodone	12 weeks	10 (100% men)	54
	3	Zisook (2000)	Nefazodone	12 weeks	19 (100% men)	NR
Other antidepressants	3	Canive (1988)	Bupropion	6 weeks	17 (100% men)	51
	2	Kaplan (1996)	Inositol	4 weeks	17 (62% men)	40
	3	Hertzberg (1996)	Trazodone	8-12 weeks	6 (100% men)	46
	3	Warner (2001)	Trazodone (adjunctive)	8 weeks	74 (100% men)	50
	2	Onder (2006)	Tianeptine	12 weeks	103 (50% men)	31
	1	Davidson (2006)	Venlafaxine	24 weeks	442 (46% men)	41
Antipsychotics	1	Hamner (2003b)	Risperidone (adjunctive)	5 weeks	40 (100% men)	51
	1	Bartzokis (2005)	Risperidone (adjunctive)	16 weeks	65 (100% men)	52
	1	Krystal et al. (2011)	Risperidone (adjunctive)	24 weeks	247 (96.6% men)	54.4
	1	Padala (2006)	Risperidone (monotherapy)	12 weeks	20 (100% women)	41
	3	David (2004)	Risperidone (adjunctive)	12 weeks	17 (100% men)	54
	3	Kozaric-Kovacic (2005)	Risperidone (monotherapy)	6 weeks	27 (100% men)	37
	3	David (2006)	Risperidone (adjunctive)	12 weeks	20 (100% men)	54
	1	Carey et al. (2012)	Olanzapine	8 weeks	28 (60.7% female)	40.75
	3	Pivac (2004)	Olanzapine	6 weeks	28 (100% men)	37
Antipsychotics	3	Petty (2001)	Olanzapine (monotherapy)	8 weeks	30 (100% men)	50

Population	PTSD SX	% Improvement Total PTSD Sx		Response Rates		Efficacy on Subscales and Comorbid Symptoms				
mixed civilian trauma, primarily sexual abuse	CAPS	72.3%		NR		NR	yes	yes	yes	yes
combat veterans	CAPS	36.2%		NR		yes	yes	no	no	no
combat veterans	IES	32.1%		NR		yes	yes	yes	yes	yes
mixed civilian trauma	CAPS	39.4%	37.6%	NR	NR	yes	yes	yes	NR	NR
combat veterans	CAPS-SX	22.9%	NR	45%	NR	no	yes	yes	yes	no
predominantly combat veterans	CAPS	23.60%	16.2%	46.00%	42.00%	no	no	yes	yes	NR
private practice, mixed trauma	SIP	46.1%		43.80%		yes	yes	yes	NR	yes
combat veterans	CAPS	28.1%		NR		yes	yes	yes	yes	NR
combat veterans	CAPS	27.0%		NR		no	no	no	no	NR
combat veterans	CAPS	31.0%		100.00%		yes	yes	yes	yes	yes
combat veterans	CAPS	18.1%		NR		no	no	yes	yes	NR
combat veterans, treatment-refractory	CAPS	31.0%		NR		no	no	NR	no	NR
combat veterans	CAPS	9.6%‡		NR		no	no	yes	yes	NR
mixed trauma, civilians and veterans, primarily accidents	IES	10.60%	–1.10%	NR		no	no	NR	no	NR
combat veterans	CAPS	14.60%		67.00%		no stats	no stats	no stats	no stats	NR
inpatient combat veterans		NR		NR		NR	NR	NR	NR	NR
civilians with trauma after earthquake	CAPS	49.4%		73.30%		yes	yes	yes	NR	NR
mixed trauma, civilians and veterans	CAPS	51.7%	43.90%	NR	NR	yes	yes	no	NR	NR
Vietnam combat veterans with psychotic symptoms	CAPS	10.00%	11.30%	NR		no	no	no	NR	NR
combat veterans medication-resistant primarily medicated	CAPS	13.70%	5.0%	41.00%	4.0%	no	no	yes	no	NR
combat veterans	CAPS	17.6%	14.1%	15.3%	6.0%	yes	no	yes	no	no
civilian women with sexual and domestic violence trauma	TOP-8	yes	yes	NR	NR	NR	NR	NR	yes	NR
Vietnam veterans, treatment resistant on stable medication	CAPS	12.8%		47.00%		yes	no	yes	no	NR
Croatian war veterans, treatment resistant with psychotic symptoms	CAPS	62.0%		NR		yes	yes	yes	yes	NR
combat veterans	CAPS	11.70%	NR	NR	NR	NR	NR	NR	NR	no
mixed civilian trauma	CAPS	57.7%	23.70%	71.4%	21.40%	no	yes	no	NR	NR
hospitalized Croatian combat veterans		NR		NR		yes	yes	yes	NR	NR
combat veterans	CAPS	29.6%		NR		yes	yes	yes	Yes	NR

(*continued*)

TABLE 19.1 (continued)

Drug Type	*Study Type*	*First Author*	*Drug*	*Duration*	*Subjects*	*Mean Age (yrs)*
	2	Kozaric-Kovacic (2007)	Quetiapine (adjunctive)	8 weeks	56 (100% men)	40
	3	Ahearn (2006)	Quetiapine (adjunctive)	8 weeks	15 (53.3% men)	49
Antipsychotics	3	Hamner (2003)	Quetiapine (adjunctive)	6 weeks	20 (95% men)	53
	3	Ahearn (2006)	Quetiapine (adjunctive)	8 weeks	15 (53.3% men)	49
	3	Pivac (2004)	Fluphenazine	6 weeks	27 (100% men)	38
	3	Mello (2008)	Aripiprazole	18 weeks	32 (25% men)	38
	3	Villareal (2007)	Aripiprazole	12 weeks	22 (82% men)	51
	3	Youssef (2012)	Aripiprazole	12 weeks	10 (50% men)	51.5
Benzodiazepine	2	Braun (1990)	Alprazolam	NR	10 (100% men)	38
	3	Cates (2004)	Clonazepam	2 weeks	6 (100% men)	NR
Anticonvulsant/mood stabilizer	2	Hertzberg (1999)	Lamotrigine	12 weeks	15 (64% men)	45
	3	Wolf (1988)	Carbamazepine	NR	10 (100% men)	37
	3	Lipper (1986)	Carbamazepine	5 weeks	10 (100% men)	38
	1	Davis (2008)	Divalproex	8 weeks	101 (98% men)	55
	3	Clark (1999)	Divalproex	8 weeks	16 (100% men)	48
	3	Bremner (2005)	Phenytoin	12 weeks	9 (55% women)	NR
	1	Davidson (2007)	Tiagabine	12 weeks	232 (no indication)	43
Anticonvulsant/mood stabilizer	3	Taylor (2003)	Tiagabine	8 weeks	7 (100% women)	40
	3	Connor (2006)	Tiagabine	12 weeks	26 (73% women)	41
	1	Tucker (2007)	Topiramate (monotherapy)	12 weeks	38 (21% men)	42
Anticonvulsant/mood stabilizer	1	Yeh (2011)	Topiramate (monotherapy)	12 weeks	31 (67.7% women)	40.4
	3	Berlant (2004)	Topiramate (adjunctive)	4 weeks	33 (85% female)	46
	3	Berlant (2004)	Topiramate (adjunctive)	4 weeks	33 (85% female)	46
	3	Alderman (2009)	Topiramate (adjunctive)	8 weeks	43 (100% men)	58
	1	Stein (2007)	Gabapentin (adjunctive)	2 weeks	48 (54% men)	29
	3	Kinrys (2006)	Levetiracetam	10 weeks	23 (39% men)	35
Sympatholytic	3	Kinzie (1994)	Clonidine	2 weeks	4 (100% men)	NR
	3	Kinzie (1989)	Clonidine, Imipramine	12+ months	9 (66.7% women)	54
	1	Taylor (2008)	Prazosin	7 weeks	13 (15% men)	49
	1	Raskind (2007)	Prazosin	8 weeks	40 (100% men)	56
	1	Raskind (2013)	Prazosin	15 week	67 (85% men)	30.4
	2	Raskind (2003)	Prazosin	20 weeks	10 (100% men)	53
	3	Raskind (2002)	Prazosin	8 weeks	59 (100% men)	59

Population	PTSD SX	% Improvement Total PTSD Sx		Response Rates		Efficacy on Subscales and Comorbid Symptoms				
combat veterans	CAPS	44.9%	NR	71.20%	NR	yes	yes	yes	NR	NR
veterans, mixed trauma, primarily sexual abuse or combat exposure	CAPS	42.0%		60.00%		yes	yes	yes	no	yes
veterans, primarily combat trauma	CAPS	24.8%		58.00%		yes	yes	yes	yes	yes
civilians and veterans, mixed trauma	CAPS	42%		20%		yes	yes	yes	yes	yes
hospitalized Croatian combat veterans		NR				yes	yes	yes	NR	NR
mixed trauma	CAPS	38%	NR	18.50%	NR	NR	NR	NR	yes	NR
combat veterans	CAPS	46.5%	NR	13.50%	NR	yes	yes	yes	yes	yes
combat veterans	CAPS	12.6%		20.00%		yes	no	yes	yes	NR
civilians and veterans, primarily combat exposure	PTSD	13.90%	4.00%	NR		no	no	NR	no	NR
combat veterans		NR		NR		NR	NR	NR	NR	NR
civilians and veterans, mixed trauma, primarily military related		NR		50.00%	25.00%	yes	no	No	NR	NR
inpatient combat veterans		NR		NR		NR	NR	NR	NR	NR
veterans, primarily combat veterans	PTSD	36.0%				yes	no	no	yes	yes
combat veterans	CAPS	20.00%	21.30%	NR	NR	no	no	no	NR	NR
combat veterans	CAPS	17.7%		NR		yes	no	yes	yes	NR
mixed trauma	CAPS	41.5%		NR		yes	yes	yes	no	yes
mixed trauma	CAPS	30.7%	0	NR	NR	NR	NR	NR	NR	NR
private practice	PCL	34.1%		86.00%		yes	yes	yes	NR	yes
mixed civilian trauma, primarily physical or sexual assault	SIP	53.9%		NR		NR	NR	NR	yes	yes
civilian trauma	CAPS	52.70%	42%	1.9	2.6	yes	no	no	no	NR
mixed civilian trauma	CAPS	72.6%	50.0%	82.4%	64.3%	yes	yes	no	no	decreased nightmares
private practice, primarily sexual or physical assault	PCL	49.0%		70%		yes	yes	yes	NR	decreased nightmares
private practice, primarily sexual or physical assault	CAPS	22.2%	NR	NR	NR	NR	NR	NR	no	NR
combat veterans	PCL-C	no	NR	NR	NR	NR	NR	NR	no	NR
civilian trauma from physical injury	PCL-C	35%	NR	0	NR	yes	yes	yes	yes	NR
civilian trauma		NR		NR		NR	NR	NR	no	NR
Cambodian refugees		NR		66.70%		NR	no	NR	yes	yes
Cambodian refugees primarily	PCL-C	12%	2.0%	26.0%	41.0%	NR	NR	NR	NR	no
civilian trauma	PCL-C	12%	2.0%	26.0%	41.0%	NR	NR	NR	NR	no
combat veterans	CAPS	17%	9.0%	24.1%	36.5%	NR	NR	NR	NR	yes
combat veterans	CAPS	32.5%	25.4%	64%	27.0%	yes	no	yes	NR	yes
combat veterans	CAPS	27.60%	–3.5%	NR		yes	yes	yes	NR	yes
combat veterans		NR		27.10%		NR	NR	NR	NR	decreased nightmares

(*continued*)

TABLE 19.1 (continued)

Drug Type	*Study Type*	*First Author*	*Drug*	*Duration*	*Subjects*	*Mean Age (yrs)*
	3	Peskind (2003)	Prazosin	8 weeks	9 (100% men)	76
	3	Taylor (2002)	Prazosin	6 weeks	5 (80% women)	48
	3	Daly (2005)	Prazosin	12 weeks	28 (96% men)	no indication
	1	Stein (2007)	Propranolol	2 weeks	48 (54% men)	29
Other	2	de Kleine (2012)	D-cycloserine	6 weeks	75 (80.6% women)	38.3
	2	Heresco-Levy (2002)	D-cycloserine	4 weeks	11 (82% men)	43
	3	Litz et al. (2012)	D-cycloserine	6 weeks	26 (100% men)	32.19
Other	3	Drake (2003)	Baclofen	8 weeks	14 (100% men)	50
	3	Lubin (2002)	Naltrexone	2 weeks	8 (75% men)	36
	2	Aerni et al. (2004)	Cortisol	4 weeks	48 (67% men)	48
	3	Saxe (2006)	Morphine	12 weeks	61 (67% men)	12
	3	Battista (2007)	Memantine	12 weeks	8 (100% men)	no indication
	1	Mithoefer (2011)	Methylenedioxy-methamphetamine	8 weeks	20 (15% men)	40.4
	3	Oehen (2013)	Methylenedioxy-methamphetamine	52 week	12 (83.3% female)	41.4
	1	Mathew (2011)	Neurokinin-1 receptor antagonist	10 weeks	39 (59% women)	40.7
	3	Golier et al. (2012)	Mifepristone	4 weeks	4 (100% men)	48.88

almost always the most common comorbid condition. Generalized anxiety disorder, dysthymia, social phobia, panic disorder, agoraphobia, and a lifetime history of alcohol or substance abuse/dependence were also common comorbid conditions. Primary psychotic disorders and active substance abuse were almost always exclusionary.

The trials were most typically completed on relatively stabilized outpatients. Thus for many studies, there were likely earlier clinical interventions related to establishing stability, assessing safety and dangerousness, engaging the trauma survivor in treatment, forming a therapeutic alliance, and treating active substance abuse that may have preceded the initiation of the treatment trials but are not specifically addressed in the studies under review.

Acute-Phase Treatment

Monoamine Oxidase Inhibitors

MAOIs were among the first medications to be systematically studied in the treatment of PTSD. An open trial of phenelzine published in 1981 noted a

Population	PTSD SX	% Improvement Total PTSD Sx		Response Rates		Efficacy on Subscales and Comorbid Symptoms				
8 combat veterans		NR		89.00%		NR	NR	NR	NR	decreased insomnia and nightmares
mixed civilian trauma	CAPS	35.70%		NR		NR	NR	NR	NR	decreased insomnia and nightmares
combat veterans	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
civilian trauma from physical injury	PCL-C	no	NR	NR	NR	NR	NR	NR	no	NR
civilians and veterans, mixed trauma	CAPS	44.4%	27.00%	63.6%	38.20%	NR	NR	NR	NR	NR
mixed civilian trauma	CAPS	–7.00%	–11.00%	NR		no	no	no	no	NR
combat veterans	CAPS	0.00%	26.70%	30.00%	70.00%	no	no	no	NR	NR
combat veterans	CAPS	23.4%		81.80%		no	yes	yes	yes	NR
civilians and veterans, mixed trauma, 50% battle trauma	RPI	4.20%		NR		no	no	no	yes	NR
mixed trauma types	CAPS	38.0%		NR		yes	possibly	no	NR	NR
children with acute injuries	Child PTSD Reaction Index	NR	NR	NR	NR	NR	NR	NR	NR	NR
combat veterans	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
civilians and combat veterans, mixed trauma	CAPS	NR	NR	83.3%	25.00%	NR	NR	NR	NR	NR
mixed civilian trauma	CAPS	NR	NR	50.00%	0.00%	NR	NR	NR	NR	NR
mixed civilian and combat trauma	CAPS	40.4%	30.0%	40.0%	21.0%	no	no	yes	NR	NR
combat veterans	CAPS	36.7%	17.2%	100%	25.0%	no	yes	no	no	NR

dramatic reduction in traumatic dreams, flashbacks, and violent outbursts in five veterans with traumatic war neurosis (Hogben & Cornfield, 1981). Subsequent studies supported this pattern of reduction in intrusive symptoms in open trials in U.S. combat veterans with PTSD (J. Davidson, Walker, & Kilts, 1987; Milanes et al., 1984). To date there have been two controlled trials of phenelzine. In a randomized, double-blind, crossover trial of 13 patients with PTSD of mixed trauma type, 4 weeks of phenelzine was not efficacious (Shestatzky, Greenberg, & Lerer, 1988). In an 8-week double-blind, placebo-controlled trial, veterans were randomized to phenelzine (60 to 75 mg/day), imipramine (200 to 300 mg/day), or placebo. Active medication was associated with significant decreases in PTSD symptoms as measured by the Impact of Events Scale (IES), particularly intrusive symptoms. The magnitude of effect was largest in the phenelzine-treated group, which experienced 68% global improvement, compared with 45% improvement with imipramine and 28% improvement with placebo. Improvement was evident in the absence of a medication effect on anxiety or depression. Thus, this was one of the first studies to demonstrate that

medications can improve PTSD symptoms independent of their antidepressant efficacy.

A disadvantage with the use of MAOIs is the necessity for diet restrictions and the risk of hypertensive crisis from tyramine-containing foods and other medications. This drawback to MAOIs has been obviated with the development of reversible inhibitors of monoamine oxidase A that do not interact with normal dietary quantities of tyramine and have a more favorable side-effect profile. Among these are moclobemide and brofaromine. In a 12-week open-label study of moclobemide in 20 patients with PTSD, significant improvement was evident in total PTSD symptoms, depression, anxiety, and overall functioning. The effect sizes were quite large, and 55% of the subjects no longer met criteria for PTSD, by far the highest remission rate reported in a medication trial in PTSD. In contrast, a controlled trial of brofaromine was negative. In a large ($N = 118$) multicenter, double-blind, parallel trial, the maximum improvement in total CAPS scores over 12 weeks was 33% in the brofaromine group and 31% in the placebo group. Of note, moclobemide is not available in the United States, and brofaromine was withdrawn from the market in 1994. Together, the data do not provide uniform support for the use of MAOIs as a class of drug in PTSD, but they do support the use of phenelzine and moclobemide in particular in the treatment of chronic PTSD.

Tricyclic and Tetracyclic Antidepressants

Prior to the introduction of SSRIs, TCAs were the most studied class of medications in PTSD. In addition to multiple positive retrospective reviews and case reports (Birkhimer, DeVane, & Muniz, 1985; Blake, 1986; Bleich, Siegel, Garb, & Lerer, 1986; Burstein et al., 1988; Falcon et al., 1985; Shen & Park, 1983; Turchan, Holmes, & Wasserman, 1992), there have been three randomized clinical trials (RCTs) of TCAs, one trial each for imipramine (Kosten, Frank, Dan, McDougle, & Giller, 1991), desipramine (Reist et al., 1989), and amitriptyline (J. R. Davidson et al., 1990).

A 4-week, double-blind, crossover study of desipramine (200 mg/day) versus placebo was conducted with 18 U.S. veterans. Desipramine treatment was associated with significant improvement in depression, but IES scores were virtually unchanged after desipramine or placebo (Reist et al., 1989). Given that it subsequently became clear that 8 weeks is the minimum duration of a treatment trial in PTSD and that there are other methodological limitations (absence of clinician-rated PTSD scales, small sample size), this negative controlled study should be considered preliminary. In the previously mentioned trial of phenelzine and imipramine (Kosten et al., 1991), 8 weeks of imipramine (200 to 300 mg/day) was superior to placebo in combat veterans with PTSD, with reduction in overall PTSD symptoms and intrusive symptoms. An 8-week trial of amitriptyline (150 to 300 mg/day) was conducted in veterans from World War II, the Korean War, or the Vietnam War with PTSD who were also receiving supportive psychotherapy (J. R. Davidson et al., 1990). Among study completers there were significant reductions in measures of anxiety and depression but no significant effect on the IES. There was a significant difference in some measures of clinical response (e.g., 50% of the amitriptyline group had a final CGI of 2 or less as compared with 16.6% of the placebo group), but not those dependent on PTSD symptom reduction (27.2% of the amitriptyline group had a greater than 50% drop in PTSD symptom score as compared with 16.6% of the placebo group). Thus, amitriptyline appears to improve clinical outcomes in PTSD, but the effect is not mediated primarily by reduction in PTSD-specific symptoms.

Several small, open-label studies have suggested that the tetracyclic antidepressant mirtazapine may be efficacious in PTSD. In six outpatients with both PTSD and major depression treated for 8 weeks, 33% showed clinical response on the CGI-I scale (Connor, Davidson, Weisler, & Ahearn, 1999). An Australian study treating 13 participants diagnosed with combat-related PTSD using a flexible mirtazapine dose (15 to 45 mg) demonstrated significant improvement assessed by both clinician- and self- administered PTSD symptom rating scales. In another, 15 patients were treated with a flexible dose of mirtazapine with significant reductions in PTSD symptoms (Bahk et al., 2002). One double-blind, placebo-controlled trial has been reported (J. R. Davidson et al., 2003). Twenty-nine patients with chronic PTSD secondary to a variety of trauma types were randomized to a fixed dose of mirtazapine (45 mg/day) for 8 weeks. The results were positive for some but not all primary outcome measures. Significantly higher response rates were found for mirtazapine than for placebo based on the global improvement measure of the Short PTSD

Rating Interview (65% vs. 22%); however, there were not significant group differences in reduction of total symptoms on this same measure. Mirtazapine was associated with greater symptom improvement in some secondary measures (Structured Interview for PTSD, Hospital Anxiety Scale) but not others (Davidson Trauma Scale, Hospital Depression Scale).

Selective Serotonin Reuptake Inhibitors

The largest type 1 studies of pharmacotherapy in PTSD have examined the efficacy of SSRIs, including fluoxetine, sertraline, and paroxetine. The first controlled trial of fluoxetine in PTSD was conducted at two different sites, an outpatient trauma clinic and a Veterans Administration (VA) outpatient clinic (van der Kolk et al., 1994). Sixty-four subjects, nearly half of whom were combat veterans, were randomized to 5 weeks of double-blind treatment with placebo or fluoxetine. For the sample as a whole, fluoxetine was superior to placebo in reducing overall PTSD symptoms. Improvement was also noted in numbing and hyperarousal symptoms but not avoidance and intrusive symptoms. The subsample from the trauma clinic had notably greater improvement than the veteran sample. In the veteran subsample, fluoxetine did not have a statistically significant effect on PTSD symptoms but did have a significant effect on depressive symptoms.

Although numerous open-label studies had suggested fluoxetine is efficacious in combat-related PTSD (Burdon, Sutker, Foulks, Crane, & Thompson, 1991; Dow & Kline, 1997; McDougle, Southwick, Charney, & James, 1991; Nagy, Morgan, Southwick, & Charney, 1993; Shay, 1992), a subsequent small, double-blind trial appeared to confirm the lack of efficacy in combat-related PTSD reported in the van der Kolk study. Twelve male Vietnam veterans were randomized to receive fluoxetine (10 to 60 mg/day; mean 48 mg/day) or placebo for 12 weeks (Hertzberg, Feldman, Beckham, Kudler, & Davidson, 2000). The response rate in the fluoxetine group was 17% as compared with 33% in the placebo group, and there were no significant fluoxetine-related differences in PTSD symptom severity measures.

Subsequent studies in civilian PTSD found fluoxetine efficacious. In a predominantly female (91%) and Caucasian (93%) sample of subjects with chronic PTSD, primarily secondary to sexual or physical assault, 12 weeks of fluoxetine was associated with significantly greater reduction in total PTSD symptom severity, evident as early as 2 weeks (Connor, Sutherland, Tupler, Malik, & Davidson, 1999). The response rate in the fluoxetine group was nonsignificantly higher than in the placebo group (85% vs. 62%), and the fluoxetine-treated group had higher end-state functioning. Another placebo-controlled trial in civilian PTSD similarly found that fluoxetine improved quality of life (Malik et al., 1999).

It was unclear whether the discrepancies in the outcome of fluoxetine treatment in civilian versus combat PTSD reflected differences in responsiveness based on trauma type or based on other factors relevant to many long-term VA patients. These include chronicity of illness, high rates of comorbid psychiatric illness and substance abuse, and even benefits and compensation seeking. A large (N = 301) double-blind, placebo-controlled trial of fluoxetine was conducted in a sample of PTSD subjects who were predominantly male (81%) and Caucasian (91%); 48% had experienced a combat-related trauma. Unlike the previous fluoxetine studies, it was not performed by the U.S. Department of Veterans Affairs but rather at sites in Belgium, Croatia, Israel, South Africa, and Yugoslavia (Martenyi et al., 2002a) in subjects who had been exposed to combat, were victims of or witnesses to war, or had witnessed another person's death. In this 12-week, flexible-dose (20 to 60 mg/day) study, the response rate in the fluoxetine group (defined as 50% or greater decrease in TOP-8 total score and a CGI-I score of much or very much improved) was 59.9%, significantly higher than the rate of 43.8% in the placebo group. The fluoxetine-treated group also had a significantly greater reduction in total PTSD symptom severity, and in particular in intrusive and hyperarousal symptoms, depression, and anxiety.

In the authors' subgroup analysis, statistically greater improvements compared with placebo were apparent in white subjects compared with nonwhite subjects, in those with combat-related PTSD compared with those with other traumas, in those with multiple traumas as compared with those with a single trauma, and in those without dissociative symptoms. The most robust effect sizes were for those without dissociative symptoms (1.20) and for those with combat-related trauma (0.78). There was a statistically significant treatment effect for men (N = 245) but not for women (N = 56); however, the effect sizes in women and men (0.53 vs. 0.35, respectively) were in the same range. These results suggest that neither

combat exposure nor male gender is associated with poor response to fluoxetine in veterans, and that combat-related PTSD may be more responsive to fluoxetine when treated earlier.

Sertraline is one of two medications approved by the U.S. Food and Drug Administration (FDA) specifically for PTSD. There have been a few large multicenter, double-blind, placebo-controlled trials of sertraline in the acute-phase treatment of chronic PTSD. One was a 12-week trial of a flexible dose of sertraline (50 to 200 mg) versus placebo in outpatients with a *DSM-III* diagnosis of moderate to severe PTSD. A total of 187 subjects were randomized. The majority were women (73%) who had physical or sexual assault as the index trauma (61.5%). Eighty-eight percent were Caucasian, and 9% were African American. The mean age of the sertraline-treated patients was 40.2 years, the mean duration of illness was 13.1 years, and the mean time from the traumatic event was 19.9 years. The prevalence of major depression was 36%, other anxiety disorders 18%, a history of alcohol abuse/dependence 22%, and a history of substance abuse/dependence 14% in the sertraline-treated group. The sertraline and placebo groups did not differ on demographic and clinical characteristics or rates of discontinuation. Of the common side effects, insomnia was significantly greater in the sertraline than the placebo group (16.0% vs. 4.3%).

Treatment with sertraline (mean dose 133.3 ± 59.2 mg/day) yielded significantly greater efficacy than placebo (based on last-observation-carried-forward analysis) on three of four a priori outcome measures: baseline–to–end point change in total CAPS scores, CGI-S, and CGI-I. There was a trend toward significant reductions on the IES scale. There was a significantly greater response rate in the sertraline than the placebo group (53% vs. 32%; defined as a greater than 30% reduction from baseline in CAPS total severity score and CGI-I score). Additionally, sertraline was associated with significantly greater improvement in depression and on multiple measures of social and occupational functioning. Sertraline did not improve reexperiencing symptoms, a core feature of the disorder, as measured on either the CAPS or the IES.

A subsequent 12-week, multicenter, controlled trial of a flexible dose (50 to 200 mg) of sertraline was conducted in a sample that was demographically and clinically similar to that of the aforementioned study (J. R. Davidson, Rothbaum, van der Kolk, Sikes, & Farfel, 2001). Treatment with sertraline was associated with a higher response rate than placebo (60% vs. 38%) and significantly greater improvement in total CAPS score, the CGI-S, and the CGI-I. As in the study by Brady and colleagues (2002), sertraline was not associated with improvement in reexperiencing symptoms; additionally, there was no improvement in hyperarousal symptoms, anxiety, or depression or on the Pittsburgh Sleep Quality Index (PSQI), a self-rated scale that assesses sleep quality and disturbances (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

There was a significant clinical response to sertraline in both studies and, as subsequently reported, a significantly higher rate of remission than placebo (23% vs. 14%; J. R. Davidson, 2004). Interestingly, sertraline was not associated with improvement in reexperiencing symptoms and was inconsistently associated with reductions in hyperarousal or depressive symptoms. This raises the question of which changes in symptoms account for the clinical improvement. A pooled analysis found that the most robust effects of sertraline were on the symptoms of emotional numbing (anhedonia, foreshortened future, emotional detachment, emotional numbing), anger, and hypervigilance (J. R. Davidson, Landerman, Farfel, & Clary, 2002). The least-affected symptoms were in the reexperiencing cluster; no significant effects were found for traumatic nightmares or physical distress at reminders, and only weak effects were observed for intrusive memories, flashbacks, avoiding feelings, insomnia, and startle. Sustained sertraline-related reductions in anger were evident by the first week of treatment and partly but not fully explained the subsequent treatment effects on the remaining symptoms. Thus, sertraline-related effects were most evident for psychologically mediated symptoms (e.g., anger, emotional distress, anhedonia) and least evident for somatically mediated symptoms (e.g., nightmares, insomnia, exaggerated startle, physiological distress; J. R. Davidson et al., 2002a).

An important limitation of these two initial sertraline studies is that a significant majority of the subjects were women, and separate analyses of efficacy were not done in men and women (although the absence of a gender-by-treatment interaction on the CAPS change scores was noted for the second study [J. R. Davidson et al., 2001]). These limitations were addressed in a similar study examining the efficacy of a daily flexible dose of sertraline (25 to 200 mg, mean = 135

mg) versus placebo in a 12-week, double-blind, multisite randomized trial (N = 169) composed primarily of males (79.9%) with an average age of 45.3 years. A change in CAPS-2 score from baseline to endpoint was their primary outcome measure. Most participants' PTSD was combat-related (71%) followed by as a result of physical or sexual assault (15.4%). The average duration of illness was 18.3 years. They found that sertraline treatment did not differ from placebo in any of their primary or secondary outcomes. They also attempted to explore whether any participant variables moderated their outcomes but did not find significance. These findings are consistent with an older study of Israeli military veterans with PTSD (N = 42), most of whom were middle-aged men (Zohar et al., 2002). In the Israeli study the index traumas were combat-related violence (N = 32), motor vehicle accidents (N = 8), and captivity (N = 2), and the mean duration of illness was 7.1 (7.8) years in those randomized to sertraline and 7.6 (8.3) years in those randomized to placebo. Subjects were randomly assigned to double-blind treatment with sertraline (flexible dose 50 to 200 mg) or placebo. Based on the intent-to-treat analysis, there were no significant differences in the change in mean CAPS, CGI-S, or CGI-I scores, and the rates of response using the same criteria as the previous sertraline studies were not significantly higher in the sertraline- than the placebo-treated group (41% vs. 20%). The small sample size does not appear to fully explain the absence of significant differences. This group of study subjects had higher baseline CAPS scores than in most studies of civilian PTSD, a lower response rate, and a smaller percentage improvement in symptoms, suggesting that sertraline may be less efficacious in male combat veterans than in other traumatized groups with PTSD.

A multisite study (N = 21 sites) examining the efficacy of sertraline on children and adolescents (6 to 17 years old, mean = 10.8) meeting criteria for PTSD had a similar lack of statistically significant findings. This study used the UCLA PTSD-I, a semistructured interview assessing the presence and severity of *DSM-IV* PTSD symptoms. One hundred thirty-one mostly female (59.7%) participants were randomized to either a flexible dose of sertraline (50 to 200 mg) or placebo. Sertraline treatment was not associated with any improvements in PTSD. Moreover, based on calculated endpoint scores using last observation carried forward, the placebo group displayed greater improvement in PTSD symptoms.

Paroxetine is the second medication to have received FDA approval for PTSD. A 12-week open-label trial of paroxetine in non–combat-related PTSD suggested efficacy in treating all three symptom clusters, as well as anxiety, depressive, and dissociative symptoms (Marshall et al., 1998). Two subsequent 12-week, double-blind, placebo-controlled trials have confirmed this. The first was a fixed-dose (20 mg/day and 40 mg/day of paroxetine) study (Marshall, Beebe, Oldham, & Zaninelli, 2001). A total of 355 patients, predominantly women who had experienced physical or sexual assault (mean age 41.8 years), completed this study. The average time elapsed since the index trauma was 15.7 years and the majority were diagnosed with a comorbid mood or anxiety disorder.

Based on an intent-to-treat analysis, improvement was significantly greater for the paroxetine groups compared with the placebo groups on all primary efficacy measures, including the CAPS total severity score and each of the three symptom cluster scores. Response rates, based on the CGI-I, were significantly greater in the paroxetine-treated groups (54% in the 40-mg/day group, 62% in the 20-mg/day group) than in the placebo group (37%), but a dose–response relationship was not evident. There was also evidence of functional improvement in the paroxetine-treated groups in the areas of work, social life, and family life. Both men and women showed significant drug-versus-placebo differences in total scores on the CAPS.

In the second paroxetine trial, 307 outpatients with a *DSM-IV* diagnosis of PTSD were randomized to either placebo or a flexible dose (20 to 50 mg/day) of paroxetine (Tucker et al., 2001). The subject characteristics were similar to those in the aforementioned paroxetine trial. Compared with the placebo group, the paroxetine-treated group (mean dose 27.6 [6.72] mg/day) showed significantly greater reduction in total severity of PTSD symptoms, in each of the PTSD symptom cluster scores, and in depressive symptoms, and showed greater functional improvement. Paroxetine was associated with higher rates of response (based on the CGI-I) and remission (CAPS total score of less than 20), and 58.8% of paroxetine-treated subjects responded and 29.4% remitted, as compared with 38.0% and 16.5%, respectively, of the placebo-treated subjects. In men and women, paroxetine treatment was associated with a statistically significantly greater change in symptoms, and equal proportions of men and women achieved

responder status. Lastly, Marshall and colleagues (2007) conducted a trial of paroxetine in a small sample of underrepresented minority outpatients with PTSD. In addition to a significant reduction in CAPS score, paroxetine treatment was associated with a reduction in dissociative symptoms and interpersonal problems.

Multiple open-label studies with fluvoxamine have been reported (J. R. Davidson, Weisler, Malik, & Tupler, 1998b; Escalona, Canive, Calais, & Davidson, 2002; Marmar et al., 1996; Neylan et al., 2001; Tucker et al., 2000). Included are studies of civilian and combat-related trauma. Each study reported significant improvement in symptoms from baseline, ranging from 32% to 72%. Improvements in reexperiencing and avoidance were found in all studies, and all but one (Escalona et al., 2002) reported improvement in hyperarousal.

Two studies have examined the effects of fluvoxamine on sleep in greater detail. In combat veterans, improvement was evident in all domains of subjective sleep quality, and especially in combat-related dreams (Neylan et al., 2001). In a study of civilian PTSD, the mean number of hours slept increased from 4.5 to 6.8 hours per night, and there was a significant decrease in sleep difficulties and trauma-related dreams (Tucker et al., 2000). Controlled trials are needed to examine whether fluvoxamine does indeed have efficacy for all PTSD symptom clusters and whether there are beneficial effects on sleep and nightmares, which have not been evident with other SSRIs.

Other Antidepressants

Nefazodone is a unique antidepressant that acts as a presynaptic serotonin reuptake inhibitor and a postsynaptic 5-hydroxytryptamine 2A (5HT2A) receptor antagonist. It has been of particular interest in PTSD because it has been shown to improve objective measures of sleep quality in depressed subjects (Rush et al., 1998). To date there have been five open-label studies in veterans; in all, treatment was associated with significant improvement in clinician-rated total PTSD symptoms, as well as in the three individual classes of symptoms (Davis, Nugent, Murray, Kramer, & Petty, 2000; Garfield, Fichtner, Leveroni, & Mahableshwarkar, 2001; Hertzberg, Feldman, Beckham, Moore, & Davidson, 1998; Neylan et al., 2003; Zisook et al., 2000). A similar pattern of improvement was observed in a sample of private practice patients (J. R. Davidson, Weisler, Malik, & Connor, 1998a). Based on ambulatory polysomnography, improvements in objective measures of sleep quality were observed with nefazodone treatment in Vietnam combat veterans. The improvements included increases in total sleep time and sleep maintenance and in delta sleep (Neylan et al., 2003), with corresponding improvements in subjective sleep quality (reductions in nightmares and improved scores on the PSQI).

The results of a 12-week, placebo-controlled, double-blind study in combat veterans were less encouraging. Although the nefazodone group showed greater improvement in global PTSD symptoms and depression, response rates in the nefazodone group did not differ from those in the placebo group at study end point (46% vs. 40%; Davis et al., 2004). Safety concerns limit the use of nefazodone as a first-line agent. It has a black box warning regarding an increased (but rare) risk of liver failure that has resulted in deaths and transplantation. Accordingly, it has been taken off the market in some countries.

Beneficial effects of venlafaxine have been noted in a case report (Hamner & Frueh, 1998) and case series (Smajkic et al., 2001). A 12-week, multisite, double-blind, randomized trial examined the efficacy of venlafaxine extended-release, a serotonin norepinephrine reuptake inhibitor approved by the FDA to treat major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder with or without agoraphobia. The overall sample consisted of 538 males and females prescribed flexible doses of sertraline (25 to 200 mg/d), venlafaxine extended-release (37.5 to 300 mg/day), or placebo. They found significant improvement in the CAPS total score for the venlafaxine group (sertraline was not significant). Venlafaxine also significantly reduced CAPS avoidance and hyperarousal scores as well as scores on the Davidson Trauma Scale (DTS; J. R. Davidson, Tharwani, & Connor, 2002b), CGI-S, and the Hamilton Rating Scale for Depression (HAM-D). Sertraline compared to placebo was only associated with improved CAPS avoidance and CGI-S.

To date there is limited information about the efficacy of bupropion as a treatment for PTSD. However, the extant data on bupropion suggest it is not an effective pharmacological treatment approach specifically for PTSD. An open-label trial of bupropion in combat veterans with PTSD found significant improvement in depressive symptoms, but not in PTSD symptoms,

except for hyperarousal symptoms. Of the 14 study completers, 10 were classified as treatment responders (Canive, Clark, Calais, Qualls, & Tuason, 1998). A small 8-week placebo-controlled, double-blind study examining the efficacy of bupropion sustained-release on a sample of men and women (N = 30, mean age = 50), diagnosed with civilian or military PTSD, did not find any significantly different reductions in PTSD symptoms.

Antipsychotics

There are scant case reports on the use of first-generation antipsychotics in PTSD (chlorpromazine: Leber, Malek, D'Agostino, & Adelman, 1999; thioridazine: Dillard, Bendfeldt, & Jernigan, 1993) and one open-label study suggesting levomepromazine improves sleep in inpatients with PTSD (Aukst-Margetic, Margetic, Tosic, & Bilic-Prcic, 2004). Given the general impression that they are not effective against core PTSD symptoms and owing to the risk of tardive dyskinesia, their use has generally not been advocated in PTSD. However, in the past decade there have been a number of trials suggesting that second-generation antipsychotics (SGAs; atypical antipsychotics) may have a role in the treatment of chronic PTSD. Among the agents studied have been risperidone, olanzapine, quetiapine, and aripiprazole.

A primary rationale for testing the efficacy of SGAs is that many patients with PTSD do not respond to first-line psychopharmacological treatments or have residual distressing symptoms and functional impairment. Accordingly, trials of these drugs initially were conducted primarily in combat veterans, treatment-resistant patients, and those with co-occurring psychotic symptoms. Assessments of outcome generally include changes in psychotic symptoms based on scales typically used for schizophrenia, such as the Positive and Negative Symptoms of Schizophrenia Scale (PANSS; Kay, Fiszbein, & Opler, 1987) and the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). Possible sides effects, such as tardive dyskinesia, akathisia, and other extrapyramidal symptoms, are typically assessed using the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976), the Barnes Akathisia Scale (Barnes, 1989), and the Simpson-Angus Scale (SAS) (Simpson & Angus, 1970), respectively.

To date there have been two open-label (David, De Faria, Lapeyra, & Mellman, 2004; David, De Faria, & Mellman, 2006), and five double-blind placebo-controlled trials (Bartzokis, Lu, Turner, Mintz, & Saunders, 2005; Hamner et al., 2003b; Kozaric-Kovacic, Pivac, Muck-Seler, & Rothbaum, 2005; Padala et al., 2006) of risperidone in combat-related PTSD. The open-label study prescribed 12 weeks of adjunctive risperidone (1 to 3 mg/day) to treatment-resistant veterans and found a significant reduction in total CAPS score, total PANSS score (as well as PANSS measures of general psychopathology, positive symptoms, and negative symptoms), and the CGI-S. With respect to safety concerns, fasting glucose levels showed a trend-level increase from baseline to endpoint, one subject gained 25 lbs, and there were no significant extrapyramidal symptom increases. A second open-label 12-week flexible-dose trial evaluated how risperidone might improve sleep in veterans with PTSD (David, De Faria, & Mellman, 2006). Participants reported decreases in trauma-related dreams as well as a decrease in the frequency of awakening in the middle of the night in the morning log assessment, and data from the sleep log indicated a reduction in the proportion of traumatic dreams by week 6 of the study.

A 6-week trial of risperidone (2 to 4 mg/day) as monotherapy was conducted among 26 treatment-resistant inpatient combat veterans. The study excluded participants with Axis I comorbidity or a family history of psychosis (Kozaric-Kovacic et al., 2005). They found a significant decrease in the total and subscale scores of the PANSS, PTSD-I, and the CGI-S. Of note, 12% of participants gained weight during the trial and 42% developed extrapyramidal side effects. A subsequent risperidone trial was conducted over a 12-week period and compared a flexible dose of risperidone to placebo (monotherapy) in 20 females between the ages of 19 and 65 years diagnosed with chronic PTSD due to sexual assault or domestic violence (Padala et al., 2006). Participants who received risperidone were started on 0.5 mg twice daily, and the dose was titrated to 1 mg daily each week to achieve a dosage of 4 to 6 mg daily. The treatment group had a significant decrease in both the total CAPS-2 score and among the hyperarousal and intrusive subscale scores.

A longer 16-week, double-blind, placebo-controlled trial of adjunctive risperidone was conducted on 65 veterans with combat-related PTSD (Bartzokis et al.,

2005). Risperidone was associated with significant reductions in total CAPS score and the psychotic subscale of the PANSS. The treatment was well tolerated and was not associated with changes in the BAS, AIMS, or SAS, adjusted for baseline scores, or with alterations in weight, heart rate, or blood pressure. Another randomized, double-blind, 5-week trial of adjunctive risperidone (1 to 6 mg/day, mean = 2.5 mg/day) was conducted on combat-related PTSD with psychotic features in the absence of a primary psychotic disorder (Hamner et al., 2003b). Examples of psychotic symptoms included auditory or visual hallucinations pertaining to the precipitating trauma or experiencing nonspecific symptoms such as hearing whispering voices or expressing paranoid ideation. Although the risperidone group displayed a significantly greater reduction on the PANSS total and global psychopathology scores, no significant changes were discovered on the PANSS positive symptom score or on total CAPS score. While there were no treatment-associated changes on the BAS, AIMS, or SAS, one patient developed akathisia.

One small, double-blind, placebo-controlled study of adjunctive risperidone (0.5 to 8 mg/day) conducted on women with moderate to severe PTSD related to childhood abuse found that risperidone treatment was associated with significant overall PTSD symptom reduction, including reexperiencing and hyperarousal (Reich, Winternitz, Hennen, Watts, & Stanculescu, 2004). In terms of adverse side effects, risperidone was associated with an increase in prolactin and no difference in weight gain compared to placebo.

Conversely, a larger 6-week, double-blind, placebo-controlled study of adjunctive risperidone (titrated to 3 mg at bedtime), conducted on 247 veterans with PTSD recruited from 23 VA outpatient centers, found that risperidone treatment was not associated with any significant CAPS score reductions and did not reduce symptoms of anxiety or depression. Adverse events were also more common in the risperidone treatment group when compared to the placebo group, including higher rates of weight gain (15.3% vs. 2.3%) and higher rates of fatigue (13.7% vs. 0%).

Olanzapine has been studied as a monotherapeutic (Carey, Suliman, Ganesan, Seedat, & Stein, 2012; Petty et al., 2001) and adjunctive agent (Stein, Kline, & Matloff, 2002) in combat-related PTSD. Petty and colleagues (2001) treated a sample of 48 veterans with open-label olanzapine (5 to 20 mg/day) for 8 weeks as monotherapy. They found a significant reduction in total CAPS score and in each of the subscales, in the BPRS, and on measures of anxiety and depression. There were no significant changes in safety measures (BAS, AIMS, and SAS). Notably, however, among completers, the mean weight gain was 3.5 ± 3.1 kg. Olanzapine was later studied as a monotherapy in an 8-week double-blind, placebo-controlled trial of 28 males and females diagnosed with non–combat-related PTSD (Carey et al., 2012). From baseline to endpoint, the olanzapine group demonstrated a significant reduction in CAPS score compared to the placebo group. Substantial weight gain (13 to 22 lbs) was reported in the treatment group.

In an 8-week double-blind, placebo-controlled trial of adjunctive olanzapine (10 to 20 mg/day) in SSRI-resistant combat veterans with PTSD (Stein et al., 2002), olanzapine treatment was associated with significantly greater reductions in total PTSD symptoms, depressive symptoms, and sleep quality. The response rates in the olanzapine- and placebo-treated groups (30% vs. 11%) were not significantly different. Weight gain, however, was significantly greater in the olanzapine than the placebo group (+13.2 lbs vs. –3.0 lbs). A double-blind, placebo-controlled trial of olanzapine monotherapy (5 to 20 mg/day) was conducted in female veterans with PTSD, primarily stemming from sexual assault/harassment in the military (Butterfield et al., 2001). The response rate (60%), extent of PTSD symptom reduction, and functional improvement did not differ between the groups. However, the olanzapine-treated group had significantly greater weight gain than the placebo group (11.5 ± 4.43 lbs vs. 0.9 ± 0.06 lbs).

To date there have not been any controlled trials of quetiapine, but there is preliminary evidence from three open-label trials suggesting it may be efficacious in chronic PTSD. In a case series of five medication-resistant PTSD subjects, all showed improvement in flashbacks with quetiapine (Filteau, Leblanc, & Bouchard, 2003). In a 6-week open-label study in combat veterans, adjunctive quetiapine (25 to 300 mg/day; Hamner et al., 2003a) was associated with a broad spectrum of improvement, including significant reductions in total PTSD symptom severity (and in each of the three symptom clusters), PANSS composite and positive symptom score, and the HAM-D. Fifty-eight percent of subjects met criteria for response based on the CGI. No significant

changes were observed for weight or blood pressures or in the AIMS, BAS, and SAS scales. Analysis of the sleep data from this study revealed significant improvement with quetiapine on multiple measures of the PSQI, most notably sleep duration, which increased from 4.0 ± 1.0 to 6.0 ± 1.8 hours per night, and sleep quality (Robert et al., 2005).

In another open-label study, quetiapine (100 to 400 mg/day) was added to the regimen of 15 PTSD patients on stable doses of SSRIs. There was a significant reduction in total CAPS score (and in each of the subscales), as well as on multiple secondary measures including the PSQI and HAM-D. Fifty-three percent of patients had a clinical response, and one went into remission (Ahearn, Mussey, Johnson, Krohn, & Krahn, 2006). There were no reports of adverse events, movement-related disorders, or weight gain.

In an additional 8-week open-label trial of quetiapine (25 to 400 mg/daily; mean = 335.75 mg/daily), 53 male inpatient veterans diagnosed with PTSD with psychotic symptoms were treated. Significant reductions in CAPS, PANSS, and CGI-S scores were found, and improvement was evident as early as week 2. In the treatment group, sedation was the most frequently reported (39.6%) adverse event, followed by hypotension (3.8%), psychomotor agitation (9.4%), and QT prolongation (5.7%) (Kozaric-Kovacic & Pivac, 2007).

To date there have been three open-label trials of aripiprazole for the treatment of PTSD (Mello et al., 2008; Villarreal et al., 2007; Youssef et al., 2012). The first was conducted over a 12-week period; 22 veterans with PTSD received 5 to 30 mg/day (Villarreal et al., 2007). Participants demonstrated significant reductions in CAPS total score and scores on subscales as well as on measures of depression, anxiety, and psychotic symptoms. Additionally, they reported an increase in sleep duration. Among the completers, 36% were responders based on a 30% or greater reduction in total CAPS score. Somnolence (54.5%), restlessness (50%), insomnia (36.4%), and asthenia (31.8%) were the most common adverse events.

Similar findings were discovered in a 16-week open-label trial of aripiprazole (7.5 to 15 mg/daily) among 32 individuals diagnosed with PTSD (Mello et al., 2008). Overall, participants had a 38% total CAPS score reduction. More than half were considered responders and had a 30% total CAPS score. Of note is the high percentage (28%) of participants who discontinued treatment prior to the second assessment; 18.7% of these discontinuations were attributed to adverse events, which included anxiety, nausea, insomnia, and psychomotor agitation.

A third 12-week open-label pilot trial of aripiprazole (5 to 30 mg/daily) conducted on 10 veterans diagnosed with PTSD also found significant decreases in total CAPS scores and other symptom outcome measures (Youssef et al., 2012). Overall, 50% of participants responded to aripiprazole, defined as a 20% reduction in CAPS score. They also had significant improvements on the Short PTSD Rating Interview (SPRINT), TOP-8, DTS, CGI-I, and all three PANSS subscales. The most commonly reported adverse effects included weight gain, concentration difficulties, and akathisia.

Positive case reports of the effect of clozapine (Hamner, 1996) and ziprasidone (Siddiqui, Marcil, Bhatia, Ramaswamy, & Petty, 2005) on combat-related PTSD have also been published.

In summary, the effects of SGAs on core PTSD symptoms and associated symptoms are mixed, although the available evidence from studies of 6 to 16 weeks' duration suggests that there may be a role for SGAs as adjunctive medications for treatment-refractory PTSD and PTSD with psychotic symptoms. The apparent efficacy of some agents, such as olanzapine, against a broad array of PTSD-specific and associated symptoms makes them a possibly attractive option. However, they do not appear to be effective in veterans. Furthermore, side effects were evident, and weight gain was especially marked for several agents and was consistently observed with olanzapine even in these short-term studies. Given the link between SGAs, weight gain, and the metabolic syndrome, the risks of treatment with SGAs in PTSD need to be carefully balanced against the potential benefits, and careful monitoring of both therapeutic effects and adverse effects is warranted.

Despite the mixed data on efficacy and the concerns regarding adverse side effects, the use of these antipsychotic medications in clinical practice is widespread. In an observational study of veterans receiving care at a VA hospital, 9% of the 831 inpatients and 10% of the 554 outpatients with PTSD were being treated with antipsychotics. In both samples, those treated with the antipsychotics had more psychiatric and social impairment. However, outcomes at 1-year follow-up were not different between those treated with and without antipsychotics (Sernyak, Kosten,

Fontana, & Rosenheck, 2001). In a nonveteran community clinic, 17% of those with PTSD alone and 34% of those with PTSD and major depressive disorder were being treated with atypical antipsychotics (Mellman, Clark, & Peacock, 2003).In an examination of VA records of 274,297 veterans with a PTSD diagnosis in 2004, 80.4% were prescribed psychotropic medication (Mohamed & Rosenheck, 2008). Among them, 33.6% were prescribed antipsychotics. Given their widespread use and potentially serious side effects, continued study is needed to examine their efficacy, which groups may be at increased risk for harm, and how the risks can be managed and minimized.

Benzodiazepines

Benzodiazepines have generally not been recommended as a treatment for PTSD owing to concerns related to efficacy, the potential for abuse and dependence, and the potential for severe symptom exacerbation with discontinuation (Risse et al., 1990). However, they have been little studied. In a double-blind, crossover trial of 10 PTSD patients of mixed trauma type, 5 weeks of alprazolam treatment was compared with 5 weeks of placebo treatment. Alprazolam was associated with significant decreases in the Hamilton anxiety scale, but no differences were observed on clinician-rated or self-rated PTSD scales (Braun, Greenberg, Dasberg, & Lerer, 1990). A randomized, single-blind, placebo-controlled crossover study of clonazepam for sleep was conducted in a small number ($N = 6$) of combat veterans. Marginal efficacy was found for clonazepam, with mild to moderate improvements in difficulty falling or staying asleep, no change in the frequency or intensity of nightmares, and little improvement in the quality of sleep (Cates, Bishop, Davis, Lowe, & Woolley, 2004).

The paucity of studies of benzodiazepines in chronic PTSD is striking in light of the frequency with which these drugs are prescribed in clinical practice. A follow-up of 370 veterans after a brief hospitalization for PTSD showed that 45% of those without substance abuse histories and 26% of those with substance abuse histories were treated with benzodiazepines (Kosten, Fontana, Sernyak, & Rosenheck, 2000). There was no evidence that benzodiazepines had an adverse effect on 1-year outcomes. Nor was there evidence that they were associated with improvement in anxiety symptoms or functioning. However, benzodiazepine use was significantly associated with lower health care utilization (Kosten et al., 2000). Understanding the mechanisms that mediate this effect is important because PTSD is associated with significant medical morbidity and very high rates of health care utilization.

This prescribing pattern is not unique to the VA. Based on a review of Medicaid records, in a community-based sample in New Hampshire, 41% of patients with PTSD alone were prescribed benzodiazepines or other hypnotics, and 54% of patients with both MDD and PTSD were treated with benzodiazepines or related hypnotics (Mellman, Clark, & Peacock, 2003). Given this vast discrepancy between treatment guidelines and actual clinical practice, large-scale, double-blind studies are needed to evaluate whether benzodiazepines are effective, deleterious, or neither in chronic PTSD. A broader range of outcomes may be needed to capture whether there is some other aspect of mental health (e.g., sense of well-being, decreased somatization) that might explain their widespread use and their apparent impact on reducing health care utilization.

Mood Stabilizers and Anticonvulsants

The use of anticonvulsants and mood stabilizers in the treatment of PTSD has been of interest for clinical reasons, since PTSD can be associated with affective instability (Golier, Yehuda, Schmeidler, & Siever, 2001), irritability, violence and other symptoms for which mood stabilizers have previously been found to be effective. Researchers hypothesize that kindling perpetuates PTSD-related symptoms (Post, Weiss, Smith, Li, & McCann, 1997). Following trauma exposure, sensitization may occur such that limbic structures subsequently respond to less intense trauma-related stimuli. This phenomenon is thought to explain reexperiencing symptoms and increased levels of distress and physiological reactions to traumatic reminders (Post et al., 1997). Raising the neuronal threshold for arousal in limbic areas could relieve the behavioral and neurobiological sensitization of trauma survivors (Keck, McElroy, & Friedman, 1992). This notion has prompted interest in the use of mood stabilizers in this disorder, including those that act on gamma-aminobutyric acid (GABA)-A (e.g., valproate) and GABA-B (e.g., carbamazepine)

receptors resulting in neuronal hyperpolarization and stabilization.

The beneficial effects of carbamazepine or its analogue oxcarbazepine have been noted in case reports (Ford, 1996; Malek-Ahmadi & Hanretta, 2004) and in a case series in which Vietnam War veterans were noted to have improved impulse control and fewer angry outbursts (Wolf, Alavi, & Mosnaim, 1988). In an open-label trial, 10 combat veteran inpatients with PTSD were treated with carbamazepine at doses ranging from 600 to 1,000 mg/day (Lipper et al., 1986), resulting in significant reductions in total PTSD symptoms and on the BPRS, as well as reductions in somatization, hostility, psychosis, and confusion-bewilderment on self-rating scales. Seven of the 10 showed a clinical response based on the CGI-I. To date, there have not been any type 1 studies examining the use of carbamazepine as a pharmacological intervention for PTSD.

Valproate has been studied in two open-label studies of combat veterans with PTSD. In the first, improvement in hyperarousal, sleep, and avoidant symptoms was noted in a group of 16 combat veterans treated with 750 to 1,750 mg/day of valproate over a period of several months (Fesler, 1991). In another, following 8 weeks of adjunctive valproate (1,000 to 2,500 mg/day; mean = 1,356 mg) there were significant decreases in total CAPS scores (including intrusive and hyperarousal symptoms), depression, and anxiety, and 11 of 13 subjects showed a clinical response (Clark, Canive, Calais, Qualls, & Tuason, 1999). A subsequent randomized, double-blind, placebo-controlled study of 82 predominantly male combat veterans, receiving a titrated dosage of 500 mg of valproate twice daily for 8 weeks, did not report significant differences in CAPS score reductions between the placebo and control groups. This was true for both total and hyperarousal cluster symptom scores, which were the specific outcome measures for this study (Davis et al., 2008).

Several reports suggest that gabapentin, approved by the FDA for the treatment of partial complex seizures and neuropathic pain, may be efficacious, especially for intrusive symptoms. In one case report, it significantly reduced flashbacks in a woman with PTSD and MDD (Malek-Ahmadi, 2003); in another, it reduced nightmares in a man with treatment-resistant PTSD following an electrical injury (Brannon, Labbate, & Huber, 2000). In a retrospective review of Vietnam veterans with chronic PTSD, 73% of subjects were rated as moderately to much improved with the addition of gabapentin, with an improvement in insomnia and nightmares (Hamner, Brodrick, & Labbate, 2001). A small randomized double-blind placebo-controlled trial comparing propranolol (discussed in the Secondary Prevention section) and gabapentin among 48 civilians with physical injury trauma prescribed to prevent the development of mental health sequelae (within 48 hours of their trauma) did not demonstrate any significant benefits of gabapentin over placebo in any of their follow-up outcome measures (Stein et al., 2007).

Topiramate is a novel antiepileptic with a broad spectrum of pharmacological properties. In addition to its anti-kindling properties, its use in PTSD is supported by preclinical data showing that it reduces acoustic startle in animals (Khan & Liberzon, 2004) and enhances the sensitivity of the glucocorticoid receptor in PTSD patients in vitro (Yehuda et al., 2004). Not only does it have positive case reports (Berlant, 2001), but a retrospective review found that it decreased nightmares in 79% and flashbacks in 86% of patients with civilian PTSD (Berlant & van Kammen, 2002). In a prospective open-label study of 33 PTSD patients in private practice, topiramate was used primarily as an adjunctive agent over 4 weeks at a median dose of 50 mg/day. Despite the short duration of treatment, significant reductions were observed in total PTSD symptoms (and in each symptom cluster) based on the self-reported PTSD Checklist. Seventy-seven percent responded, with a 30% or greater reduction in PTSD symptoms. With respect to intrusive symptoms, 79% ceased having reexperiencing symptoms, with a mean time to full cessation of just 15 days. These encouraging initial results suggested that topiramate might have a rapid rate of response in PTSD, but subsequent and more rigorous studies have been equivocal about its efficacy. A double-blind randomized control trial on 38 mostly female outpatients did not demonstrate a statistically significant reduction of PTSD symptoms as measured by the CAPS (Tucker et al., 2007). Yet a more recent double-blind study found a significant (–57.78% vs. –32.41%) reduction of CAPS score in their sample of 35 civilians diagnosed with PTSD (Yeh et al., 2011). There appears to be a paucity of studies with large sample sizes in the current topiramate literature.

Tiagabine is a selective GABA reuptake inhibitor that increases extracellular GABA levels. In addition to a positive case report (Berigan, 2002) and case series (Taylor, 2003), an open-label study of tiagabine (mean dose 12.5 ± 4.0 mg/day) was completed in patients with chronic PTSD (Connor, Davidson, Weisler, Zhang, & Abraham, 2006). Among completers, there was significant improvement in PTSD symptom severity, anxiety, depression, sleep quality, and level of functioning. However, a subsequent type 1 study has called into question these initial promising results (J. R. Davidson et al., 2007). A 12-week double-blind, placebo-controlled continuation phase trial of 232 participants found that CAPS total score reductions from baseline to termination did not differ significantly between the treatment and placebo groups (30.7 vs. 30.2 points).

Phenytoin is an anticonvulsant that blocks the cellular responses to glutamate. Interest in phenytoin in the treatment of PTSD was prompted by observations that the deleterious effects of stress on memory performance and the hippocampus in animals are blocked by phenytoin (Hui, Guang-Yu, Chong-Tao, Quan, & Xiao-Hu, 2005; Watanabe, Gould, Cameron, Daniels, & McEwen, 1992). To the extent that PTSD symptoms or the associated neuropsychological impairments and neuroanatomical alterations (Bremner et al., 1997; Gurvits et al., 1996) are mediated by similar effects of stress on humans, phenytoin could theoretically attenuate this process (Bremner et al., 2005). In an open-label study of phenytoin as monotherapy, 9 of 12 patients completed the study. Among completers there was a 41.5% reduction in total CAPS score and a significant reduction in all three PTSD symptom clusters, in the absence of significant reduction in anxiety or depression. Social and occupational functioning also improved. RCTs are necessary to establish the certainty of phenytoin's efficacy as a pharmacological treatment of PTSD.

Information about the efficacy of lithium carbonate in the treatment of PTSD is also scant in the literature. Van der Kolk (1983) performed an open trial of lithium carbonate (therapeutic dose: 300 to 1,500 mg/day) in 14 treatment-refractory combat veterans. Eight of them improved, with noted reduction of hyperarousal symptoms. Kitchner and Greenstein (1985) reported similarly beneficial results in an open trial with five combat veterans. A recent case study found a significant reduction of acute suicidality among two female patients with PTSD treated with 3 to 4 weeks of lithium carbonate at 600 to 900 mg daily.

In summary, multiple anticonvulsants and mood stabilizers with varying neurobiological mechanisms have been tested for the treatment of PTSD and have demonstrated mixed efficacy outcomes. While these treatment approaches have been promising, there is a lack of type 1 trials to fully ascertain their utility as pharmacological interventions for PTSD.

Sympatholytic Agents

Interest in the potential use of antiadrenergic drugs in PTSD dates back to some of the earliest scientific observations regarding the pathophysiology of this illness. Beginning with Kardiner's (1941) seminal depiction of "physioneurosis" in combat veterans, there has been evidence of increased sympathetic nervous system activation in PTSD. Abundant lines of evidence support this view, including evidence of elevated levels of catecholamines (Kosten, Mason, Giller, Ostroff, & Harkness, 1987), enhanced autonomic responses to loud tones (Orr, Lasko, Shalev, & Pitman, 1995), and increased alpha-2 receptor sensitivity (Southwick et al., 1999).

The possibility that sympatholytic antihypertensives could be effective against chronic PTSD was investigated as early as 1984. Kolb, Burris, and Griffiths (1984) studied propranolol, a nonselective beta-adrenergic receptor blocker, in 12 Vietnam combat veterans. At doses of 120 to 160 mg/day there was improvement in explosiveness, nightmares, intrusive recollections, startle response, hyperalertness, and impaired sleep, as well as in self-esteem and psychosocial function. Propranolol was also noted in a case report to reduce the reemergence of PTSD symptoms following retraumatization (Taylor & Cahill, 2002). Stein and colleagues (2007) investigated the efficacy of propranolol (120 mg/daily for 14 days after trauma exposure) as a preventive intervention for PTSD (discussed in greater detail in the Secondary Prevention section). They found that propranolol was not significantly better than placebo on any of their outcome measures.

Kolb and colleagues (1984) also reported that clonidine, an alpha-2 receptor agonist, alleviated flashbacks and hyperarousal in combat veterans. Clonidine is of particular interest, since subsequent studies have demonstrated that the alpha-2 receptor antagonist yohimbine exacerbates PTSD symptoms in

the laboratory and in naturalistic settings (Southwick et al., 1997, 1999). In a pilot study, Kinzie, Sack, and Riley (1994) added clonidine to the treatment of nine Cambodian refugees with PTSD who did not improve with imipramine and followed them for 12 to 19 months. In this descriptive study the researchers noted that six of the patients had improvement in PTSD symptoms (two no longer met criteria for the disorder), six had improvement in sleep, six had improvement in depression, and seven had improvement in nightmares.

Prazosin, a centrally active adrenergic-1 antagonist, has been more extensively studied. Following up on a clinical observation, an initial case series using this sympatholytic antihypertensive in combat PTSD showed that at low doses at bedtime, prazosin improved severe and chronic combat-related nightmares (Raskind et al., 2000). In a small open-label trial in civilian PTSD, 6 weeks of prazosin was also associated with clinical improvement and reduction in nightmares (Taylor & Raskind, 2002). In a retrospective review of 58 male Vietnam and Gulf War veterans with treatment-refractory PTSD, those treated with at least 8 weeks of prazosin (mean dose = 9.6 ± 0.9 mg/day) showed a significant decrease in distressing dreams (Raskind et al., 2002). Of the few published studies of PTSD treatment in the elderly, prazosin reduced nightmares in elderly combat veterans and a Holocaust survivor (Peskind, Bonner, Hoff, & Raskind, 2003).

Treatment with prazosin was subsequently evaluated in a double-blind, placebo-controlled, crossover trial in 10 Vietnam War combat veterans with chronic PTSD and severe nightmares. For most subjects it was an adjunctive agent. Not only was improvement in sleep difficulty and recurrent distressing dreams noted, but there were significant reductions in the PTSD total score and scores on each of the three subscales. Furthermore, prazosin treatment was associated with greater clinical global improvement than placebo (Raskind et al., 2003).

Prazosin is emerging as an effective treatment for the sleep problems and nightmares associated with PTSD and may be useful for a broader range of PTSD symptomology. Indeed, appreciation of the benefit of this medication is suggested by Bernardy, Lund, Alexander, and Friedman (2012), who estimate that the prescription of prazosin among veterans has increased by 9.1% (almost seven-fold) from 1999 to 2009. A more recent double-blind randomized trial (n = 34) found significant improvement of PTSD sleep-related symptomology among male combat veterans who took the study drug for 8 weeks (Raskind et al., 2007). The study team expanded upon these initial results with a larger trial of 56 participants aimed at understanding the impact prazosin has on sleep quality in male veterans (Raskind et al., 2013). Prazosin was determined to significantly improve nightmare symptoms of PTSD, supported by reductions in both CAPS sleep questions and the PSQI. This drug is unique in targeting a specific subset of PTSD symptoms. Further research is needed to develop targeted PTSD psychopharmacological interventions for sleep and other specific distressing symptoms.

Despite the compelling scientific rationale for the use of sympatholytic agents, to date there have been no randomized, double-blind, placebo-controlled trials investigating the independent effects of clonidine on PTSD symptoms. Furthermore, neither of the two studies of guanfacine (type 1 and type 3) has demonstrated significant reduction in CAPS scores following treatment (Davis et al., 2008; Neylan et al., 2006). The need for future research of sympatholytic agents is further suggested by the promising early outcomes with prazosin. Such studies may help us to better understand whether direct modulation of the noradrenergic system in PTSD is associated with a clinically meaningful treatment response.

Sedatives and Hypnotics

Disrupted sleep, which can be characterized by difficulties initiating and maintaining sleep, distressing nightmares, and phobic avoidance secondary to nightmares, is often a chronic and distressing symptom in PTSD. Research has been devoted to better understand the unique qualities of sleep disturbances in those diagnosed with PTSD. Findings indicate a high prevalence of nightmares (compared to sleep onset and maintenance insomnia) and have been replicated across several studies (Neylan et al., 1998; True et al., 1993). Sleep quality and quantity have rarely been measured by type 1 and type 2 drug trials for PTSD. However, sleep improvements have been noted in open-label studies with fluvoxamine, nefazodone, and tiagabine (Connor et al., 2006; Neylan et al., 2001; Rush et al., 1998; Tucker et al., 2000). Additionally, quetiapine treatment was associated with significant improvement on multiple

measures of the PSQI, most notably sleep duration, which increased from 4.0 ± 1.0 to 6.0 ± 1.8 hours per night, and sleep quality (Robert et al., 2005). However, since monotherapy is rarely sufficient to improve PTSD sleep-related disturbances, sedative/hypnotics are frequently prescribed as an adjunctive agent. Despite this, few empirical data are available to guide prescribers.

Trazodone is a triazolopyridine antidepressant with sedative effects that has been evaluated in two uncontrolled trials. The larger of the two is a survey of the adjunctive use of trazodone in combat veteran inpatients ($N = 74$; Warner, Dorn, & Peabody, 2001). Nineteen percent discontinued trazodone, with the most common adverse side effects being daytime sedation and priapism (the latter occurred in 12% of subjects). Seventy-two percent of the patients who continued taking trazodone (mean dose = 212 mg/day) found that it decreased nightmares, 92% found that it aided sleep onset, and 78% reported improvement in sleep maintenance.

Zolpidem tartrate, zaleplon, and eszopiclone are nonbenzodiazepine hypnotics specifically indicated for insomnia (Ancoli-Israel, Walsh, Mangano, & Fujimori, 1999; Dieperink & Drogemuller, 1999; Pollack et al., 2011). Among these, eszopiclone is the only hypnotic that has been approved for long-term use. A type 1 efficacy study of 24 civilians found that those who were prescribed eszopiclone had significantly lower CAPS total and PSQI scores at endpoint compared to placebo (Pollack et al., 2011). It is remarkable that a sedative can lead to global improvements in PTSD symptomatology, and the mechanism requires further study. This finding raises the possibility that sleep improvement itself can lead to broader therapeutic gains, or that the medication itself has effects beyond sedation. Still, further investigation of other nonbenzodiazepine hypnotics is necessary, especially since preliminary studies, such as a clinical report on zolpidem in chronic PTSD, showed success in treating insomnia without adverse effects for as long as 20 months (Dieperink & Drogemuller, 1999).

Despite the limited study of anxiolytics and sedative/hypnotics for PTSD patients (and guidelines that discourage their use) actual use remains widespread. Approximately 61% of veterans prescribed psychotropic medications receive this drug class; prescriptions are mostly associated with a comorbid anxiety disorder diagnosis (Mohamed & Rosenheck, 2008). According to Bernardy, Lund, Alexander, and Friedman (2012), rates of prescription of nonbenzodiazepine hypnotics remained relatively stable until 2008, when there was a tripling of prescriptions, coinciding with zolpidem's placement on the national VA formulary. These prescribing trends highlight the need for more rigorous research on the potential benefits and harms of sedative/hypnotic use in PTSD.

Novel Agents

Decades of work by VA investigators and others have demonstrated that dysregulation of the HPA axis is a feature of PTSD pathophysiology and an important potential biological treatment target (discussed at length in the Secondary Prevention section). The question arises as to whether or how this knowledge can identify novel biological targets for PTSD that might reduce PTSD symptoms. Of particular interest in this regard is mifepristone (RU 486), a potent glucocorticoid receptor antagonist. This glucocorticoid receptor antagonist is hypothesized to recalibrate the HPA axis through blockade of peripheral and central GR while enhancing central glucocorticoid signaling. Mifepristone is also thought to potentially have beneficial neurocognitive-enhancing properties. Young and colleagues (2004) reported significant spatial working memory and verbal fluency improvements based on a trial of 20 participants with bipolar disorder. A mifepristone crossover trial of 32 Gulf War veterans found that low-dose mifepristone (200 mg daily) prescribed for 6 weeks significantly improved verbal learning compared to placebo (Golier et al., 2014).

There are limited studies examining the impact of mifepristone on PTSD. One pilot study explored the efficacy of mifepristone as a brief (week-long) PTSD pharmacological intervention. Mifepristone was prescribed once daily (600 mg) for 7 days via a double-blind, placebo-controlled, all-male-veteran sample ($N = 8$). At endpoint the treatment group demonstrated a statistically greater clinical response (defined as a decrease in CAPS2 total score of at least 12) than the placebo group, and one participant no longer met criteria for PTSD. These results suggest that mifepristone may have the potential to be a short-term, time-limited, pharmacological intervention for the treatment of acute and long-term PTSD symptomology (Golier et al., 2012). These results have informed a VA-sponsored multisite, double-blind, controlled trial that is under way to examine the efficacy and safety of short-term mifepristone in military PTSD.

Some researchers have hypothesized that treating glutamatergic sites in the brain may be a beneficial treatment approach for PTSD (Charney et al., 1993; Friedman, 2000; Nutt, 2000), since glutamate is implicated in learning and memory (Collingridge & Bliss, 1995) and stressful memories are associated with activation of the *N*-methyl-D-aspartic acid (NMDA) glutamate receptors (Glue et al., 1993). D-cycloserine (DCS) is a broad-spectrum antibiotic and antitubercular drug and a selective partial agonist at the glycine site on the NMDA receptor. In a double-blind, placebo-controlled, crossover study of 11 patients with PTSD, symptom improvement with DCS (25 mg bid) was not significantly better than placebo (Heresco-Levy et al., 2002).

A subsequent 6-week, double-blind, placebo-controlled crossover study used D-serine (30 mg/kg/d), an NMDA full agonist, on 22 mostly medicated outpatients with chronic PTSD and showed a similar lack of findings. Participants reported reductions in anxiety based on the HAM-A, self-reported PTSD symptoms assessed by the MISS, and a reduction on the CAPS reexperiencing cluster. This was the first study conducted on D-serine, and further research is warranted to understand the implications of potentially treating PTSD (Heresco-Levy et al., 2009).

Buspirone, a nonbenzodiazepine anxiolytic, has been reported as effective in a case study describing three combat veterans (Wells et al., 1991). Buspirone (dose range 35 to 60 mg) reduced associative symptoms of anxiety and depression, as well as insomnia and flashbacks. Finally, there are a few clinical reports in which the serotonin antagonist cyproheptadine was used successfully for the treatment of traumatic nightmares (Brophy, 1991; Harsch, 1986) in the dosage range of 4 to 28 mg/day.

Summary of the Results of Acute-Phase Treatment Trials of Chronic Posttraumatic Stress Disorder

In summary, this review of the existing literature shows that, based on type 1 and type 2 studies, monotherapy with phenelzine, imipramine, sertraline, fluoxetine, paroxetine, and olanzapine has been shown to be effective in the treatment of PTSD, as compared with placebo, based on both improvements in total PTSD symptom severity and higher response rates. Despite these results, some other studies examining the efficacy of sertraline, phenelzine, and fluoxetine have found mixed results. Despite their scant utilization, amitriptyline and mirtazapine have both been demonstrated to be superior to placebo with respect to clinical response but not total PTSD symptom reductions. Other negative controlled trials have been reported for brofaromine, desipramine, inositol, and alprazolam. The results from the brofaromine study appear to be conclusive. Results for the other three agents are not definitive, given the small sample sizes (10 to 18 subjects) and, for the latter three agents, the short trial duration (5 weeks or less).

In terms of SSRIs, paroxetine consistently demonstrated efficacy against all three PTSD symptom clusters. In contrast, sertraline is not effective in reducing reexperiencing symptoms and was associated with decreased hyperarousal and decreased depressive symptoms. For fluoxetine the pattern of efficacy for the individual symptom clusters were not consistent across studies. There are also varying results from controlled trials examining the effectiveness of anticonvulsants and sympatholytics in alleviating PTSD symptoms. While they show promise as adjunctive medications for the reduction of reexperiencing and hyperarousal symptoms, additional controlled trials with larger sample sizes are needed to fully determine their efficacy.

In general, risperidone, olanzapine, and prazosin appear to be effective adjunctive treatments in treatment-resistant or refractory patients. Recent open-label trials of aripiprazole also show promising results. All were associated with significant reductions in total PTSD symptoms. Reduction in PTSD-related psychotic symptoms was noted with the SGAs and with distressing nightmares with prazosin. However, the risk/benefit ratio of the SGAs needs to be very carefully weighed because both extrapyramidal and metabolic adverse side effects were significant even during short-term trials.

Very few of the controlled trials in PTSD specifically assessed sleep quality or quantity; however, in controlled trials prazosin and eszopiclone have been shown to be beneficial in targeting sleep (Pollack et al., 2011; Raskind et al., 2003), and there are indications that risperidone and clonazepam may improve sleep in PTSD by reducing trauma-related dreams, helping with sleep-onset problems, and improving one's ability to stay asleep (Cates et al., 2004; David, De Faria, & Mellman, 2006). Although SSRIs are considered a first-line treatment, they have not been shown to have beneficial effects on sleep quality in PTSD, and sertraline was associated with a significantly greater

occurrence of insomnia as an adverse side effect in civilian PTSD (J. R. Davidson et al., 2001).

Maintenance Treatment and Relapse Prevention

Prescribers now have available a number of pharmacological approaches to treating PTSD. Partial response is a more typical outcome than complete remission, and these treatments are not curative. Thus, the question arises as to whether efficacy is maintained or enhanced over time and whether or for how long continuation treatment is indicated. Some data are available that can begin to answer these questions.

A study of continuation treatment in PTSD was conducted with sertraline. Subjects who completed the double-blind sertraline studies were eligible to continue in the open-label continuation phase lasting 24 weeks (Londborg et al., 2001). Subjects remained blinded to the acute-phase treatment during the continuation phase; 92% of responders maintained their response during the continuation phase. Importantly, 54% of those who did not achieve responder status during the acute phase achieved it during the continuation phase. High baseline symptom severity was an important predictor of longer time to response; comorbidity, childhood trauma, depression, the number of traumas, and other demographic variables were not predictors.

The final phase of this series of studies of sertraline was designed to examine whether maintenance therapy protects PTSD patients from relapse or deterioration (J. R. Davidson et al., 2001). This type 1 double-blind, placebo-controlled discontinuation study enrolled PTSD patients who had shown sustained responses at the end of the continuation phase. Maintenance treatment was continued for 28 weeks after a previous 24-week continuation study. Sertraline demonstrated a significant advantage over placebo in prevention of relapse (5.3% vs. 26.1% participants who relapsed) and acute exacerbation of PTSD symptoms (15.8% vs. 52.2%). The sample was predominantly female, but the prophylactic benefit of sertraline was evident in both men and women. These data suggest that the efficacy of sertraline treatment is maintained, sometimes enhanced over time, and can prevent exacerbations and relapse.

In a similarly designed trial, PTSD subjects who responded to acute treatment were randomized to continue in a 24-week double-blind maintenance phase on either fluoxetine ($N = 69$) or placebo ($N = 62$; Martenyi, Brown, Zhang, Koke, & Prakash, 2002). Response was stringently defined as a 50% decrease in the TOP-8 score, a CGI-S score of 2 or lower, and not meeting the criteria for PTSD. Among those who responded to fluoxetine in the acute-phase study, the completion rate in the continuation phase was higher in subjects randomized to fluoxetine than to placebo (83% vs. 66%). In a subsequent discontinuation study, PTSD subjects were randomly assigned to double-blind treatment with either fluoxetine or placebo, after having shown at least minimal response to open-label fluoxetine treatment for 6 months (up to 60 mg/day) (J. R. Davidson et al., 2005). There were a significantly higher number of relapses in the placebo group (50%) than in the fluoxetine group (22%), and a significantly earlier time to relapse in the placebo group. However, differences in relapse rates were not noted based on self-report instruments. Thus, the results from clinician- and self-report data are not entirely consistent, but the results of the two studies suggest that continued therapy with fluoxetine appears to prevent relapse as compared with placebo when categorical criteria of relapse are used based on clinician assessments.

Open-label continuation studies also provide preliminary evidence for the benefits of maintenance treatment with other antidepressants. Multiyear follow-up was obtained in an open-label trial of nefazodone in combat-related PTSD at doses of 400 to 600 mg/day (Hertzberg, Feldman, Beckham, Moore, & Davidson, 2002). Of the 10 patients who responded at the end of the 12-week trial, 7 remained "much improved," 2 were "minimally improved," and 1 was worse. In a small, open-label study of mirtazapine in PTSD, gains made during the initial 8-week trial were maintained over the 6 months of treatment, and there was an increase in the number of responders over time (Kim, Pae, Chae, Jun, & Bahk, 2005). Taken together, these studies suggest that treatment gains in PTSD are maintained or enhanced during maintenance treatment with antidepressants, and antidepressants are indicated in the long-term management of this chronic disorder, as they are in other affective and anxiety disorders.

Nevertheless, patients with PTSD are known to have high rates of nonadherence to pharmacological treatments (Chilcoat & Breslau, 1998). Research into the reasons for this treatment obstacle is still nascent. Some preliminary findings indicate that medication adherence is related to the specific ways

that patients understand how PTSD affects them biologically and psychosocially and their perceived ability to control their symptomatology (Spoont et al., 2005). Further work is needed to determine how best to engage patients in long-term treatment and identify optimal pharmacological strategies—either alone or in combination with psychotherapy—that induce longer-lasting therapeutic effects.

Secondary Prevention of Posttraumatic Stress Disorder

Although stress and trauma are implicated as risk factors for many Axis I and II disorders, PTSD is in a unique category of trauma- and stressor-related disorders for which a traumatic event is a prerequisite. The immediate aftermath of a traumatic event represents a potential window of opportunity for early intervention to prevent the development of the full disorder. Concerns about terrorism and the effects of a number of recent natural and manmade disasters have brought the question of how to intervene clinically after a trauma into sharper focus. Educational, psychotherapeutic, and pharmacological approaches are all possible interventions that can be applied to trauma survivors at greatest risk for developing PTSD. Preliminary medication trials for the secondary prevention of PTSD have been conducted for cortisol, beta-blockers, and benzodiazepines.

Activation of the HPA axis in response to a traumatic stressor leads to the release of cortisol from the adrenal gland, which, through negative feedback inhibition, ultimately serves to constrain the stress response. There is ample evidence of HPA axis dysregulation in chronic PTSD, including elevations in corticotrophin releasing factor (Baker et al., 2005; Bremner et al., 1997), which is a potent stimulator of the stress response. However, PTSD is not typically associated with elevated serum or urinary cortisol levels. Rather, it is often, but not always, associated with reduced 24-hour cortisol levels (reviewed in Yehuda, 2002), which may cause a deficit in central negative feedback. It has been suggested that these HPA axis alterations contribute to overactivation of the HPA axis and sympathetic nervous system following stress (Yehuda., 2002). Whether HPA axis alterations are evident at the time of trauma is not known, but several prospective studies suggest that lower posttraumatic cortisol levels in the acute aftermath of trauma predict the subsequent development of PTSD (McFarlane, Atchison, & Yehuda, 1997; Resnick, Yehuda, Pitman, & Foy, 1995), whereas cortisol levels at 1 week do not (Bonne et al., 2003).

These findings raise the question of whether manipulation of the HPA axis at the time of traumatization can prevent the development of PTSD. Compelling data from studies of intensive care unit (ICU) patients suggest it can. Patients treated in the ICU provide an opportunity to study the relationship between trauma, glucocorticoids, and the subsequent development of trauma-related psychopathology, since such patients often receive exogenously administered catecholamines and glucocorticoids and have high rates of PTSD resulting from life-threatening illness and its treatment (Schelling et al., 1999). In an initial retrospective case-control comparison of septic shock patients treated in an ICU, those who had received stress doses of hydrocortisone had a lower incidence of PTSD than those who had not (5 of 27 vs. 16 of 27); they also had higher scores of emotional well-being (Schelling et al., 1999). A similar result was found in a prospective, randomized, double-blind study of the hemodynamic effects of hydrocortisone on septic shock. Development of PTSD in the group treated with stress doses of hydrocortisone (1 of 9) was significantly lower than in the placebo group (7 of 11; Schelling et al., 2001). The effect did not appear to be mediated through memory consolidation, since there were no significant group differences in the recall of categories of traumatic memories from the ICU (Schelling et al., 2001). In a randomized, double-blind, placebo-controlled pilot study of patients with acute stress symptoms, stress doses of hydrocortisone were associated with a significant reduction in the CAPS score compared with placebo, and at the 2-week follow-up assessment, 66.7% of participants as opposed to 20% of placebo group participants who were in the hydrocortisone treatment group developed acute stress reaction (Zohar et al., 2011).

This series of studies provides an interesting demonstration that direct administration of cortisol in the peritraumatic period prevents the development of PTSD secondary to life-threatening illness. Although this is a unique population and the doses of steroids used were high, the results may be more broadly applicable. In a small double-blind, crossover study of low doses of cortisol in patients with civilian PTSD, cortisol treatment effectively reduced PTSD

symptoms, especially reexperiencing symptoms (Aerni et al., 2004). Owing to the beneficial effects of hydrocortisone observed in these controlled studies, studies of the efficacy and safety of short-term cortisol treatment for the secondary and tertiary prevention of PTSD are warranted.

The use of beta-blockers in the secondary prevention of PTSD has also been explored. There is considerable evidence of overactivation of the sympathetic nervous system in PTSD and in those who are at high risk for developing PTSD after a trauma (Shalev et al., 1998; Southwick et al., 1999). Epinephrine strengthens memory consolidation, and it has been hypothesized that excessive release of epinephrine at the time of a traumatic event results in an exceptionally strong emotional memory and conditioned fear response that is ultimately manifested as symptoms of PTSD (Pitman, 1989). Propranolol, which crosses the blood–brain barrier, eliminates this memory-consolidating effect in humans (Cahill, Prins, Weber, & McGaugh, 1994) and is therefore considered a candidate for the prevention of PTSD.

To examine this hypothesis, traumatized persons at increased risk of PTSD, as reflected by a heart rate greater than 80 beats per minute at emergency room admission, were randomly assigned to a 10-day course of double-blind treatment with propranolol ($N = 18$) versus placebo ($N = 23$), 40 mg four times daily (Pitman et al., 2002). The first dose was given within hours of the event. At 1 month, the mean CAPS scores in the two groups did not differ. There was, however, one outlier with very high levels of PTSD symptoms in the propranolol group. This outlier may have obscured group differences, since the distribution of PTSD severity scores was significantly different in the two groups (Pitman et al., 2002). However, the rate of PTSD in the placebo completers was not statistically different than in the propranolol completers at 1 month (30% vs. 18%) or 3 months (13% vs. 11%).

A nonrandomized open-label study of propranolol in trauma victims was subsequently performed (Vaiva et al., 2003). Trauma survivors with tachycardia were offered treatment with propranolol 40 mg, three times a day for 7 days, and were assessed 2 months later. There was not a significant difference in the rates of PTSD in those who refused propranolol versus those who received the medication (3/8 vs. 1/11); however, PTSD symptom severity as measured by the TOP-8 was significantly lower in the propranolol than the no-propranolol group.

A double-blind randomized proof-of-concept trial of propranolol in physically injured trauma survivors was also performed (Stein, Kerridge, Dimsdale, & Hoyt, 2007). Forty-eight male (54%) and female participants with severe injuries who required emergent trauma care were randomized to receive propranolol (120 mg/day), gabapentin (1,200 mg/day) or placebo for 14 days, which included three phases: uptitration (2 days), acute treatment (8 days), and the taper phase (4 days). Participants were assessed at 1, 4, and 8 weeks following the injury. While they did not demonstrate any significant findings, of the 569 potential participants, only 8% consented to the treatment.

Thus, neither preliminary study shows that propranolol protects against the development of a diagnosis of PTSD, but it may reduce the severity of PTSD symptoms in the months following trauma. Larger controlled trials are needed to definitively answer this question, since the ability to prevent the development of PTSD has important ramifications for public health.

Finally, three studies have examined the effect of benzodiazepines in recent trauma survivors. The use of benzodiazepines in the aftermath of trauma is rooted in the idea that they reduce arousal, inhibit memory consolidation, and have antipanic properties (Gelpin et al., 1996). In a study of consecutive emergency room admissions, trauma survivors who reported excessive distress within the first week after a traumatic event were treated at the discretion of the research psychiatrist with either clonazepam or alprazolam and interviewed at successive points after the traumatic event (Gelpin et al., 1996). Their posttraumatic symptoms were compared with those of a control group drawn from an ongoing study and matched by gender and PTSD symptoms at 1 week. The benzodiazepine-treated group did not differ from the comparison group in PTSD or depressive symptoms at multiple assessments over 6 months. Thus, within the limits of a case-control design, this study does not suggest a beneficial effect of benzodiazepines on the course of PTSD; rather, the development of PTSD was higher in the benzodiazepine-treated group. Considering the nonrandom assignment to the treatment group, it cannot be concluded that benzodiazepines facilitated the development of PTSD.

In a pilot evaluation of temazepam in four subjects with acute symptoms following trauma, temazepam was administered for 5 nights, tapered for 2 nights, and then discontinued. At 1 week, sleep had

been improved and PTSD symptom severity lessened (Mellman, Byers, & Augenstein, 1998). In a subsequent randomized, placebo-controlled trial, 22 trauma survivors manifesting early symptoms of PTSD were randomly assigned to placebo or temazepam for 7 nights, beginning on average 14 days after the trauma. There was no improvement in sleep parameters in the temazepam group beyond its period of use (Mellman et al., 1998). However, 55% of the subjects in the temazepam group and 27% of subjects in the placebo group had PTSD at final assessment. None of these studies provides definitive or even suggestive evidence that the short-term use of benzodiazepines in the acute treatment of trauma is beneficial. The higher rate of PTSD development in the benzodiazepine-treated group in both the case-control and the randomized trial suggests that such treatment may in fact be deleterious. Yet a clear recommendation cannot be made on the basis of these results. Larger studies are needed to determine whether the seemingly innocuous act of prescribing a benzodiazepine in the short term to an acutely distressed trauma survivor might indeed be helpful or ultimately have adverse effects on the natural course of posttraumatic recovery.

ADJUNCTIVE DRUG THERAPY: PAIRING PHARMACOLOGICAL TREATMENTS WITH PSYCHOTHERAPY

Psychotherapeutic techniques can be equally important for the maintenance of PTSD remission, relapse prevention, and even secondary prevention in the aftermath of a traumatic event. Yet there is still a dearth of empirical evidence on how or when to combine pharmacological treatment and psychotherapy. It is unclear when or whether the combination is superior to either treatment alone or whether one treatment modality can treat residual symptoms following a course of treatment with the other modality. Recently, however, certain pharmacological agents have shown potential for short-term enhancement of psychotherapy outcomes.

Propranolol and other sympatholytic agents may be particularly efficacious in reducing the physiological symptoms of PTSD when paired with psychotherapy. One study tested propranolol on 19 civilians with mixed trauma. The participants underwent psychophysiological script-driven imagery therapy, which required them to read a script of their trauma. Immediately following this, they were administered 40 mg of short-acting propranolol followed by 60 mg of long-acting propranolol 2 hours later. One week later, they were asked to read the same script again. The researchers found that those who were given the two doses of propranolol 1 week prior to the assessment had significantly decreased physiological arousal (heart rate and skin conductance level) compared to the placebo group (Brunet et al., 2008).

Another promising agent to be used in conjunction with therapy is DCS (discussed earlier in the section on novel agents), a partial NMDA receptor agonist that has been implicated with improved extinction of fear in animal studies (Walker, Ressler, Lu, & Davis, 2002). While DCS has been shown to have positive outcomes with some diagnoses—such as improved outcomes in acrophobics undergoing behavioral exposure therapy (Ressler et al., 2004)—its efficacy in PTSD has been mixed. In one randomized, double-blind, placebo-controlled trial, 67 participants with military and/or civilian trauma were each given a 50-mg dose of DCS 1 hour before weekly sessions of prolonged exposure therapy (de Kleine et al., 2012). At treatment follow-up, completers showed an average CAPS total score reduction of 23% and general clinical response, but this decrease did not significantly differ from placebo. Moreover, a concurrent randomized placebo-controlled trial of 26 military veterans found that those who were prescribed placebo in conjunction with exposure therapy had greater CAPS score improvements than those who took DCS with therapy (36.4% vs. 33.3%, respectively) (Litz et al., 2012). Another recent study, conducted on 22 mostly male (76%) participants with mixed civilian trauma, demonstrated that those who received 100 mg of DCS 90 minutes before virtual reality exposure therapy differed significantly from the placebo group on mean CAPS score reduction (45.9% vs. 30.0%, respectively). This between-groups difference increased over time, with peak values at the 6-month follow-up. Clearly, further investigation is necessary into the efficacy of DCS when paired with psychotherapies, including expanding the size and enhancing the diversity of sample populations.

While investigations are still in the early pilot phase, hydrocortisone has also been implicated as a novel adjunctive pharmacological treatment for prolonged exposure therapy, particularly for the modification of trauma-related memories and learning. An

initial case report consisting of one male veteran given 300 mg of oral hydrocortisone 30 minutes before each of seven prolonged exposure sessions and another male veteran given placebo demonstrated that the treated but not the untreated participant had a significantly greater reduction in the CAPS total score (52 vs. 42 points) (Yehuda et al., 2010). Although limited by the sample size of only two participants and other metrics of study design rigor, this observation suggests the potential for cortisol treatments adjunctive to behavioral interventions for PTSD. Another concurrent double-blind, placebo-controlled study tested the impact of hydrocortisone treatment on Cluster C (cognitive and memory) PTSD symptoms. They found a significant between-groups difference (drug = 1.9 vs. placebo = 2.7) (Surís et al., 2010).

Preliminary studies suggest that the potential benefit of nontraditional approaches—such as the use of 4-methylenedioxymethamephetamine (MDMA)—in addition to psychotherapy may be efficacious in the treatment of PTSD (Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011; Oehen, Traber, Widmer, & Schnyder, 2013). MDMA is thought to be particularly compatible with psychotherapy since it is short-acting and produces feelings of acceptance and of being emotionally grounded (Doblin, 2002). In the first RCT of MDMA (125 mg at first dose; 62.5 mg supplemental dose) paired with psychotherapy in 20 participants with chronic treatment-resistant PTSD, there was a significant decrease in CAPS scores for the treatment group at all three time points following baseline (Mithoefer et al., 2011). Eighty-three percent of the treatment group had a significant clinical response versus 25% in the placebo group. For the entire duration of the study, no serious adverse events, adverse neurocognitive impacts, or significant increases in blood pressure were reported. In a randomized, double-blind, active-placebo controlled pilot study of MDMA-assisted psychotherapy, 12 participants with PTSD were randomized to a low-dose group (25 mg, plus 12.5 mg supplemental dose) and a full-dose group (125 mg, plus 62.5 mg supplemental dose). While the change in the CAPS score between the two groups was only marginally significant ($p = 0.066$), there were statistically significant improvements in the Posttraumatic Diagnostic Scale scores. There were also significant changes in the CAPS score observed between the second and third psychotherapy sessions in the full-dose group (Oehen et al., 2013). Still, the fate and acceptance of treatment with this low-dose psychedelic remain unknown. The possibility of acceptance is suggested by the emerging mainstream use of intravenous ketamine—an NMDA antagonist and drug of abuse (i.e., "Special K")—in depression and possibly PTSD, informed by evidence that ketamine reduces symptoms of depression and anxiety (Aan het Rot, Charney, & Mathew, 2008; Berman et al., 2000; Clinicaltrials.gov, 2012; Zarate et al., 2006) and suicidality (Price, Nock, Charney, & Mathew, 2009). McGhee, Maani, Garza, Gaylord, and Black (2007) found that ketamine, given to Operation Enduring Freedom/Operation Iraqi Freedom veterans prior to surgery, was related to a lower rate of the subsequent development of PTSD. Most recently, Feder and colleagues (2014) compared intravenous ketamine infusions (0.5 mg/kg) to infusions of an active control, the benzodiazepine midazolam (0.045 mg/kg), in 45 veterans with PTSD. They reported that ketamine produced a greater reduction in symptoms measured by the IES-R scale than midazolam 24 hours after the infusions. Furthermore, with the relaxation of laws prohibiting marijuana use, it is likely that medical marijuana will be explored as a potential PTSD treatment. In an open-label clinical trial of synthetic cannabinoid in the management of PTSD, 72% of participants reported a reduction in the intensity and frequency of nightmares (Fraser, 2009). Further research into cannabinoid use for the treatment of PTSD is under way in several countries.

Fortunately, the pace of PTSD treatment advances over the past 5 to 10 years is promising and will likely continue to yield more effective (and novel) treatments for this disorder in the coming years.

PRESCRIBING TRENDS AND FUTURE DIRECTIONS

The numerous type 1 and type 2 studies in PTSD completed in recent years support the view that pharmacotherapy can be a primary treatment for chronic PTSD. Evidence from such studies suggests that multiple antidepressants from different classes are effective first-line agents in the acute phase and maintenance treatment of PTSD, especially but not only SSRIs and serotonin/norepinephrine reuptake inhibitors. Some SGAs are also effective adjunctive treatments for a broad range of symptoms in treatment-refractory PTSD, although the benefits need be measured against the risks.

As new information becomes available, and as providers develop their own body of experience treating PTSD, prescribing practices change. An analysis of the change in prescribing of different classes of medications in the VA (Bernardy, Lund, Alexander, & Friedman, 2012) from 2004 to 2009 highlights some of these trends. While there was only a small change in overall antidepressant use (net absolute change in frequency of use of +2.7%), there were significant shifts in the types of agents prescribed. There was a significant increase in use of SSRIs or serotonin/norepinephrine reuptake inhibitors (+9.3%) as well as an increase in the use of mirtazapine (+7.4%) and bupropion (+5.6%) and significant decreases in the use of the TCAs (–10.0%) and nefazodone (–11.7%).

In contrast, overall antipsychotic use decreased significantly during this period. The reduction was driven primarily by decreased use of first-generation antipsychotics (–7.5%) and little change in overall use of SGAs. A notable exception to this latter trend was a significant increase in prescriptions for low-dose quetiapine (+9.1%). Benzodiazepine use decreased (–6.1%), but this change was accompanied by increased use of prescriptions to aid sleep, namely marked increases in the use of nonbenzodiazepine hypnotics (+9.1%) after zolpidem was placed on the national formulary, a dramatic increase in prazosin use (+7.7%), and the aforementioned increase in quetiapine, which is sometimes used clinically for sleep enhancement in PTSD.

These data reflect both a trend toward prescribing informed by the literature on efficacy as well as an openness to prescribe medications off-label for symptoms for which effective treatments are under studied or still needed (e.g., insomnia). Despite the substantial gains made, much more needs to be done to expand the pharmacological options available to treat this potentially chronic and disabling disorder.

While drug treatment for acute-phase PTSD is certainly critical, there is increasing appreciation about the chronicity of this disorder for some trauma survivors and the associated burdens. There is therefore a need to develop and test pharmacological and other strategies for sustained management and diminution of chronic PTSD symptoms. Additional studies are also needed to determine ways to maximize the efficacy of existing treatments, whether through determination of optimal dosing and duration of treatment or by combining different agents. Much more information is needed on predictors of response to different agents to facilitate treatment matching for this heterogeneous disorder. Future studies also need to address the clinical needs of subjects not included in these studies, including geriatric patients, PTSD patients with active substance abuse, and patients with severe mental illness in whom PTSD may be a secondary but distressing condition.

Finally, almost all the agents shown to be effective in PTSD were developed and marketed for other illnesses and have secondarily been demonstrated to be useful in the treatment of PTSD. To profit from the advances made in the psychobiology of PTSD, it is important to conduct rigorous trials of medications whose use is supported by a strong theoretical basis from either preclinical or human biological studies.

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Treatments for Eating Disorders

Kathleen M. Pike
Loren M. Gianini
Katharine L. Loeb
Daniel Le Grange

Substantial progress in advancing evidence-based treatments for eating disorders has been made, although significant gaps in knowledge remain that require further attention. Many well-designed type 1 and type 2 studies provide cumulative support for cognitive-behavioral therapy (CBT) as the treatment of choice for bulimia nervosa (BN). A significant body of research also supports the utility of Interpersonal psychotherapy (IPT) and pharmacotherapy in the treatment of BN; they are considered appropriate alternative treatments for BN in cases where CBT has not been effective or is contraindicated. While CBT, IPT, and pharmacotherapy often produce significant reductions in binge eating and compensatory behaviors, there remains a need to improve upon these treatment outcomes to help more individuals achieve full and lasting recovery. In the treatment of binge eating disorder (BED), CBT and IPT have been shown to be the most efficacious in reducing symptoms and improving psychological outcomes. Weight loss is often an additional goal of those entering treatment for BED; however, existing treatments have generally been unsuccessful in producing significant maintainable weight loss. Anorexia nervosa (AN) remains extremely challenging to treat. However, initial studies suggest that CBT may be associated with improved outcome both in the acute and maintenance phases of treatment. Recent findings also suggest that adapting CBT and Specialist Supportive Clinical Management (SSCM) for severe and enduring AN can result in better engagement in treatment and significant clinical improvement. Additional, methodologically rigorous studies are needed to more fully inform treatment guidelines for adults with AN. Family-based treatment employing the Maudsley Model has shown promising results for adolescents with a relatively short-term duration of illness.

INTRODUCTION

Eating disorders are prevalent psychiatric conditions that are associated with life-threatening medical complications, comorbid psychiatric disorders, role impairment, and suicidality (Crow et al., 2009; Swanson et al., 2011). In particular, AN has the highest mortality rate of any psychiatric disorder. These disorders typically begin in adolescence or early adulthood and, when untreated, often follow a severe and enduring course (Wonderlich et al., 2012). Over the past decades, an enormous amount of clinical research has been conducted that provides important data to guide treatment across the spectrum of eating disorders. At the same time, significant gaps exist in terms of developing evidence-based guidelines for the range of eating disorders, and more clinical research is necessary to address essential questions of clinical care and treatment.

This chapter begins with a diagnostic update that highlights the changes brought about by the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*). This material is followed by a detailed review of available evidence for both pharmacotherapy and psychotherapy for the main eating disorders: AN, BN, and BED. The clinical implications of the available treatments for each of these diagnoses are summarized.

DIAGNOSTIC UPDATE

Anorexia Nervosa

AN typically begins in adolescence or young adulthood and predominantly affects females (about 10% of cases are male). AN is less common than either BN or BED; the 12-month prevalence among young females is approximately 0.4% (Hoek, 2006).

DSM-IV criteria for AN were widely viewed as overly restrictive and, as such, diagnostic criteria for *DSM-5* have been broadened to capture common variations in case presentation. In the revised diagnostic criteria of *DSM-5*, the diagnosis of AN is made if individuals restrict their energy intake such that they achieve a "significantly low weight" in relation to what would be expected for individuals of the same age, sex, developmental trajectory, and physical health. A body mass index (BMI) of 18.5 kg/m^2 or below is provided as a general guideline for "significantly low weight" among adults; however, it is possible for individuals to have a higher BMI and still meet criteria for AN, particularly if the individual's starting weight was especially high. For children and adolescents, there is no hard-and-fast delineation of what constitutes "significantly low weight." However, the Centers for Disease Control and Prevention defines "significantly low weight" as a BMI that falls below the fifth percentile for age (Centers for Disease Control and Prevention, 2011). In addition to low weight, individuals with AN typically demonstrate an intense fear of gaining weight or becoming fat. In addition, *DSM-5* AN includes individuals with persistent behaviors that interfere with weight gain even if they do not describe overt fear of weight gain or fat. These individuals are often referred to as having "non-fat-phobic anorexia." The allowance of behavioral indicators of the psychological features of AN renders the criteria more developmentally sensitive, as verbal endorsement of such symptoms is often absent in children and adolescents. This change is critical for early case identification and intervention in light of the age-of-onset data noted above.

Individuals with AN place undue importance on shape and weight while experiencing body image disturbance, and they often fail to appreciate the seriousness of maintaining a dangerously low weight. Given the importance of a thin shape and low weight in the self-evaluation of individuals with AN, the significantly low weight they have been able to achieve and the restrictive behaviors that maintain this weight are often viewed as ego-syntonic. As such, many individuals with AN do not pursue treatment of their own accord, and they may be resistant when concerned family or friends attempt to persuade them to attend treatment. Finally, the *DSM-5* eliminated amenorrhea as a diagnostic criterion for postmenarcheal females, given its narrow clinical applicability and poor predictive utility. Individuals with AN may be classified as either restricting or binge/purge subtypes. Severity specifiers of mild, moderate, severe, and extreme have now been added and are based upon BMI, such that lower BMI ranges connote heightened severity of illness. AN is associated with an elevated mortality rate, with the crude mortality rate being approximately 5% per decade (Smink et al., 2012). The majority of deaths are due to medical complications of the eating disorder or suicide (Arcelus et al, 2011).

Bulimia Nervosa

BN typically emerges slightly later than AN but still predominantly affects adolescents and young adult women. BN is also more common than AN, with a 12-month point prevalence of approximately of 1% to 1.5% in young females (Hoek, 2006). BN is characterized by binge eating episodes in which the individual eats an objectively large amount of food within a discrete period of time (usually less than 2 hours) *and* experiences a sense of loss of control while engaged in this behavior. These binge episodes are followed by some type of compensatory behavior, which is most often self-induced vomiting or the misuse of laxatives, but may also include use of diuretics, enemas, diet pills, excessive exercise, or fasting. When not engaged in binge eating, most individuals with BN attempt to restrict food intake in pursuit of weight loss to achieve a thin beauty ideal. Weight and shape are extremely

important to the sense of self-worth for individuals with BN, and body dissatisfaction is typically elevated. By diagnostic distinction, individuals with BN are normal weight or higher; underweight individuals who binge eat and/or purge would be characterized as having AN, binge/purge type. BN is associated with an elevated mortality rate, with the crude mortality rate being approximately 2% per decade; suicide risk is elevated in this group as well (Crow et al., 2009; Smink et al., 2012).

In *DSM-IV*, the diagnostic criteria for BN required that individuals engage in binge eating followed by inappropriate compensatory behaviors at least an average of twice a week for 3 months. This criterion has been modified in *DSM-5* such that binge eating and subsequent inappropriate compensatory behaviors must occur on average at least once a week for 3 months. This revision was made as a result of research demonstrating that the functional impairment and overvaluation of weight and shape among individuals engaging in binge/purge episodes at this lower frequency did not differ significantly from those engaging in these behaviors more frequently (Wilson & Sysko, 2009). *DSM-5* has eliminated the subtype specification of "purging type" and "nonpurging type" and has added severity specifiers of mild, moderate, severe, and extreme, which are based upon the frequency of inappropriate compensatory behaviors. The validity and utility of these severity specifiers have yet to be examined empirically.

Binge Eating Disorder

In *DSM-IV*, BED was ascribed research diagnostic criteria and classified under the umbrella diagnosis of "eating disorder not otherwise specified." There have been numerous studies since 1994 confirming that BED is deserving of its own diagnostic category; as such, BED is now a distinct diagnosis in *DSM-5*.

The hallmark feature of BED is binge eating without regular compensatory behavior (e.g., absence of vomiting, over-exercise, or laxative abuse). Binge eating occurs an average of at least once per week for at least 3 months, and individuals with BED experience distress because of their binge eating. While many individuals with BED have tried dieting on numerous occasions, the dietary restriction observed in AN and BN is not typically seen in this group. It is common for individuals with BED to be overweight or obese, particularly in clinical settings. Unlike AN and BN, the gender ratio in BED is much less skewed and the 12-month prevalence of BED is 1.6% in females and 0.8% in males (Hudson et al., 2007). The prevalence of BED is greater among obese adults (estimates range from 8% to 28%; Hudson et al., 2007) and it is greater still in obesity treatment facilities and clinics (Johnson et al., 2001; Wilfley et al., 2003). While BED may begin in adolescence and young adulthood for many, it is not uncommon to encounter many BED patients in mid- to late adulthood.

Avoidant/Restrictive Food Intake Disorder

In *DSM-5*, avoidant/restrictive food intake disorder has replaced the *DSM-IV* diagnosis of "feeding disorder of infancy and early childhood," which was rarely used in practice. These diagnoses are fairly similar; however, *DSM-5* has broadened the diagnostic criteria, thus increasing the number of identified cases and reducing the number of cases relegated to an unspecified eating disorder category. Avoidant/restrictive food intake disorder is characterized by a feeding or eating disturbance such that an individual fails to meet appropriate caloric or nutritional needs, may be dependent on tube feeding or nutritional supplements, and/or has markedly impaired psychosocial functioning, such as an inability to eat in front of others. In contrast to AN and BN, there is no evidence of significant shape and weight concerns.

Individuals with avoidant/restrictive food intake disorder may experience a lack of interest in food or an aversion to sensory qualities of foods, such as certain types of food textures, colors, or smells. These difficulties most commonly develop in infancy or early childhood and may or may not persist into adulthood (Wildes et al., 2012). Other individuals with avoidant/restrictive food intake disorder may avoid eating due to fear of aversive consequences, such as choking or vomiting. This type of food avoidance may be prompted by a traumatic event such as choking or a medical procedure such as esophagoscopy. The course of avoidant/restrictive food intake disorder is unknown, although there is some evidence that sensory-based food aversions may be lifelong (Mascola, Bryson, & Agras, 2010). It is also unclear what the relationship is between avoidant/restrictive food intake disorder and other eating disorders.

Rumination Disorder

The hallmark feature of rumination disorder is repeated regurgitation of food for at least 1 month. Once regurgitated, the food may then be rechewed, reswallowed, or spit out. The regurgitation should not be due to a medical condition, and it cannot occur exclusively in the context of another eating disorder. Onset of rumination disorder can occur at any time throughout the lifespan. Prevalence rates are unknown, but it is thought to occur more frequently in individuals with intellectual disability (Olden, 2001).

Pica

Pica is defined by the eating of nonnutritive, nonfood substances for at least 1 month. This behavior should be inappropriate to developmental level, and it is recommended that pica not be diagnosed in children younger than 2 years of age, given that it may be developmentally normal for infants to mouth nonfood objects and ingest them. If this behavior occurs in the context of another disorder, such as an intellectual disability or an autism spectrum disorder, it should be severe enough to warrant additional independent clinical attention. Childhood onset is most common, but pica can begin at any time throughout the lifespan. Although pica is occasionally related to a nutritional deficiency, this is not the case in most individuals. The general prevalence of pica is unknown; however, among individuals with an intellectual disability, the prevalence tends to increase as severity of intellectual disability increases (American Psychiatric Association, 2013). Pica can be dangerous and sometimes fatal when an individual ingests a poisonous or otherwise injurious substance.

Other Specified Feeding or Eating Disorder and Unspecified Feeding or Eating Disorder

In *DSM-5*, "other specified feeding or eating disorder" and "unspecified feeding or eating disorder" diagnoses replace the *DSM-IV* diagnosis of eating disorder not otherwise specified. "Other specified feeding or eating disorder" is intended to capture eating disorders that do not meet full criteria for the other eating disorders in this diagnostic class; they allow the clinician to describe the specific reason why it does not fit into one of these other diagnoses. One example of a presentation that would warrant a diagnosis of other specified feeding or eating disorder would be "atypical anorexia nervosa," wherein an individual meets all criteria for AN but, despite significant weight loss, still is in the normal weight range. Other common variants of other specified feeding or eating disorder are purging disorder, wherein an individual purges in an attempt to influence shape or weight but does not engage in binge eating, and night eating syndrome, wherein an individual eats excessively after his or her evening meal or after awakening from sleep during the night. A diagnosis of unspecified feeding or eating disorder should be used when the clinician chooses not to or cannot give further detail as to the nature of the eating disturbance but can confirm that the disorder causes significant distress or impairment. The prevalence of these disorders is unknown since they are new additions to the *DSM-5*.

TREATMENTS FOR ANOREXIA NERVOSA

There are several important treatment targets in AN. Of paramount importance is that patients gain weight and begin engaging in a sustainable regimen of regular, healthy eating. Relapse is common in AN, so it is also important for treatment to address the factors that put an individual at greatest risk for reactivating eating disorder behaviors, keeping in mind that cognitive symptoms often persist until full and sustained weight restoration is achieved. While there have been many studies of different treatments for AN and many more are in progress, there have been few randomized controlled trials (RCTs) and fewer conclusive answers as to best practices in treatment with this patient group.

Medically fragile and severely ill patients with AN are often treated in hospital, inpatient, or residential settings. There are a number of ethical concerns regarding randomizing these patients to conditions wherein they might receive placebos, inactive, nonspecific treatments, or be placed on a waiting list (Watson & Bulik, 2012). As such, best practices for these chronic and severe patients are typically derived from expert clinical experience and opinion rather than RCTs and often involve inpatient hospitalization.

Pharmacotherapy

Since the publication of the third edition of this volume, several RCTs have examined the impact of atypical antipsychotic medications on weight gain and eating disorder psychopathology in AN (Attia et al., 2011; Bissada, Tasca, Barber, & Bradwejn, 2008; Brambilla et al., 2007; Kafantaris et al., 2011; Mondraty et al., 2005). Among these atypical antipsychotics, olanzapine has been the most commonly studied. Taken together, the results of these studies demonstrate that the impact of atypical antipsychotics on weight gain and psychological symptoms has been mixed, inconsistent, and small in the studies in which benefits have been found.

Studies have also examined the effectiveness of fluoxetine following weight restoration in AN. A small study by Kaye and colleagues (2001) suggested that outcome may improve with use of fluoxetine. However, a larger, well-controlled RCT conducted by Walsh and colleagues (2006) found that fluoxetine did not have an impact on time to relapse, weight gain or loss, or core eating disorder pathology above and beyond CBT, and there was no evidence that it was superior to placebo. Thus, at the current time, no psychotropic medication has proven efficacy for AN treatment.

Psychotherapy

Family-Based Therapy

Family-Based Therapy (FBT; sometimes referred to as the Maudsley Method) is a manualized treatment conducted on an outpatient basis, typically spanning approximately 20 sessions over the course of 12 months (Lock & Le Grange, 2012). As part of this treatment, parents are charged with helping their child restore weight by managing their child's caloric intake throughout the day. Once weight restoration is well under way, treatment focuses on gradually transferring control over eating back to the patient, who in most studies of FBT is an adolescent. While there have been a number of open trials and clinical case series examining the utility of FBT in AN, there are few RCTs comparing FBT with another active treatment. Given the low base rate of treatment-seeking individuals with AN, it can be difficult to recruit adequate numbers of participants, and sample sizes in studies are often quite small. Furthermore, while RCTs are viewed as the most rigorous means of determining the efficacy and effectiveness of treatments, they too are imperfect. Given this caveat, we will review the RCTs of FBT below in some detail.

In the first major RCT of FBT for AN, Russell and colleagues compared the effects of 1 year of FBT versus individual therapy on maintaining weight restoration achieved in a hospital setting (1987). This research team found that FBT was superior to individual therapy at 1 year in achieving a "good" outcome, marked by maintaining at least 85% ideal body weight, and reduced eating disorder psychopathology in the subset of patients with AN who were ill for 3 years or less, and had their onset of AN at or before age 18. FBT was not superior to individual treatment in patients who had been ill for more than 3 years or who had their onset of AN at age 19 or later. The group in which a significant differential effect of treatment was found (ill for less than 3 years, onset age at or before age 18) comprised 21 patients, 11 of whom received FBT. The superiority of FBT in this subset of patients was maintained 5 years later (Eisler et al., 1997).

The second RCT comparing a family treatment similar to FBT (Behavioral Family Systems Therapy [BFST]) with an individual "ego-oriented" therapy was conducted in a sample of adolescents between the ages of 12 and 19 who had been ill for 12 months or less and were at least at 75% of ideal body weight (Robin et al., 1999). Of the 37 patients, 19 were assigned to BFST and 18 were assigned to individual "ego-oriented" therapy. BFST patients entered treatment at a lower BMI than participants in individual "ego-oriented" therapy (15.2 vs. 16.6, respectively). Treatment was 12 to 18 months in duration, and by the end of the study both intervention groups had gained a significant amount of weight. Although those in BFST gained more than those in individual "ego-oriented" therapy, at both end of treatment and at the 1-year follow-up, BFST and individual "ego-oriented" therapy did not differ significantly with regards to number of participants reaching either 50th percentile BMI or 25th percentile BMI.

More recently, Lock and colleagues (2010) conducted a significantly larger two-site RCT comparing 24 sessions of FBT to 32 sessions of Adolescent Focused Therapy (akin to individual "ego-oriented" therapy). Treatments were equivalent in therapy contact hours delivered over the course of a year in a sample of 121 adolescents aged 12 to 18 years. The

researchers defined remission as reaching at least 95% of expected body weight and having eating pathology scores within one standard deviation of community norms on the Eating Disorder Examination (EDE). At the end of treatment, remission was reached in 42% of participants in FBT and 23% in those assigned to Adolescent Focused Therapy, although this difference did not reach statistical significance. At the 6-month follow-up, remission rates were 40% and 18%, respectively, and at the 12-month follow-up they were 49% and 23%, respectively, with both differences being statistically significant. Additionally, a significantly greater number of Adolescent Focused Therapy participants were hospitalized during treatment in comparison to FBT participants (32 vs. 9), although mean number of days in the hospital and mean weight gain in the hospital did not differ by treatment group.

Several studies have compared different delivery formats for FBT. Eisler and colleagues (2000) compared conjoint family therapy, wherein the parents and the child are seen together, with separate family therapy, wherein the parents and the child are seen separately, in a sample of 40 adolescent patients with AN. Average age of patients was 15.5 years and average duration of illness was 12.9 months. There were no significant differences between these two treatment formats from pre-treatment to posttreatment in terms of percentage ideal weight, BMI, and weight change. Of note, separate therapy was significantly better than conjoint therapy in families with high expressed emotion (hostile, critical forms of communication). This advantage was sustained at the 5-year follow-up (Eisler, Simic, Russell, & Dare, 2007), with patients from families with high expressed emotion assigned to separate therapy continuing to gain weight and patients from families with high expressed emotion assigned to conjoint therapy demonstrating no significant weight changes. Le Grange and colleagues (1992) found a similar lack of overall difference in outcomes between conjoint and separate family therapy in a sample of 18 adolescents with AN.

Lock and colleagues (2005) compared two different treatment doses of FBT: 10 sessions over 6 months versus 20 sessions over 1 year. The sample comprised 86 adolescents with a mean duration of illness of approximately 12 months and a mean initial BMI of 17.1. There were no observed differences in outcome at 12 months after randomization, although patients with higher levels of eating-related obsessive-compulsive symptoms and nonintact families fared better with the longer intervention.

In sum, FBT focuses on early intervention and is particularly useful for young patients with a short duration of AN. FBT has been most widely studied in adolescents, and the literature demonstrates that it is as effective or better than other treatments. The caution and challenge for the field is to recognize that the FBT trials have been conducted by a small team of researchers, and it will be important to replicate the demonstrated utility of FBT among independent investigators and clinicians. Furthermore, the preliminary data regarding conjoint (parent and child) versus separate (parent only) treatment outcomes suggest that the format of family-based therapy interventions may need to be adjusted depending on the level of expressed emotion in the family.

Individual Psychotherapy

A number of RCTs comparing individual therapy approaches in samples of adults and adolescents with AN have been reported, although the results have not revealed a clear advantage of one treatment over another. Several small studies have compared CBT, behavior therapy, nutritional counseling, cognitive analytic therapy, and low-contact control conditions in various permutations (Channon, De Silva, Helmsley, & Perkins, 1989; Crisp et al., 1991; Hall & Crisp, 1987; Serfaty, Turkington, Heap, Ledsham, & Jolley, 1999; Treasure et al., 1995). No significant findings have emerged from these studies.

A larger study (n = 84) comparing focal psychoanalytic psychotherapy, cognitive analytic therapy, FBT, and routine outpatient treatment involving brief sessions found no significant differences in outcome between the three active treatments, although all three were superior to routine outpatient treatment (Dare, Eisler, Russell, Treasure, & Dodge, 2001). These participants were older (mean age = 26.3 years), and the mean duration of illness was 6.3 years. "Good" outcomes were achieved in only 13.8% of the sample, which is significantly worse than outcomes in many studies among the cohort of younger patients with a shorter duration of illness.

McIntosh and colleagues (2005) studied 56 adult women with AN (diagnosed without applying the *DSM-IV* amenorrhea criterion) plus 23 with subthreshold AN (BMI 17.5 to 19.0) by randomizing

them to 20 sessions of CBT, IPT, or SSCM. Results showed that SSCM was superior to IPT; CBT fell between SSCM and IPT and was not statistically different from either of the other two treatments. This sample was evaluated again approximately 7 years later; at that point all three treatment groups were equivalent on physical, cognitive, and behavioral measures of AN (Carter et al., 2011). Overall, 49% of the sample had a good outcome.

A multisite trial comparing CBT, fluoxetine, and their combination randomized 122 patients with AN; however, only 37% completed the 1-year study (Halmi et al., 2005). Notably, 73% of patients in the fluoxetine-alone condition did not complete the treatment, and the low completion rates overall did not allow the authors to assess and compare outcomes. The retention challenges in this study call attention to the difficult nature of studying and treating AN.

More recently Schmidt and colleagues (2012) developed a treatment for adult AN (Maudsley Model of Anorexia Nervosa Treatment for Adults [MANTRA]). MANTRA focuses on the health risks inherent in AN, the often-present rigid cognitive style, the function of AN in the patient's life, and behavioral experiments to address socioemotional difficulties. MANTRA was compared to SSCM in an RCT with 72 outpatients with AN or eating disorder not otherwise specified. Recovery was defined in three ways: (A) eating pathology within one standard deviation of community norms on the EDE, (B) BMI above 18.5, and (C) both A and B. The proportion of MANTRA patients meeting criterion A at posttreatment and at the 6-month follow-up was 43% and 59%, respectively, compared to 45% and 73% in the SSCM group. The proportion of MANTRA patients meeting criterion B at posttreatment and at the 6-month follow-up was 18% and 27%, respectively, compared to 21% and 26% in the SSCM group. Finally, the proportion of MANTRA patients with both normal EDE scores and BMI above 18.5 at posttreatment and at the 6-month follow-up was 7% and 14%, respectively, compared to 13% and 19% in the SSCM group. There were no statistically significant differences between the two treatment outcomes.

The largest RCT to date in adults with AN randomized 242 individuals to focal psychodynamic psychotherapy, enhanced CBT, or treatment as usual (Zipfel et al., 2014). The treatment-as-usual condition is notable in that it was conducted within the context of the German health care system and participants were given the names of experienced eating disorder therapists, with sessions typically being covered by health insurance. These treatment-as-usual patients also met with a medical provider to have regular weights and blood tests. By the end of treatment, 22% of patients had dropped out, and by the 12-month follow-up a total of 30% had dropped out. While BMI did increase across all treatment groups and eating pathology decreased at both end of treatment and again at the 12-month follow-up, no significant differences emerged across the treatment conditions.

Relapse Prevention and Severe and Enduring Anorexia Nervosa

There have been a small number of studies examining the effects of psychological treatment on weight-restored patients after hospitalization. As reported above, Russell and colleagues (1987) compared the impact of FBT and supportive psychotherapy in a sample of adolescents and adults with AN after weight restoration in hospital. As noted, the young, short-duration cases fared better if they received FBT; however, the older patients with a longer duration of illness did poorly across conditions. There have been two studies evaluating the impact of CBT versus an active comparison treatment after hospitalization. In the first study, 33 patients were randomized to either 12 months of CBT or nutritional counseling (Pike, Walsh, Vitousek, Wilson, & Bauer, 2003). In the CBT group, 44.4% achieved an adapted Morgan Russell outcome of "good" (BMI ≥ 18.5 for 8 consecutive weeks, cyclical menses, but some disturbance in weight concern, restraint, or binge/purge behaviors) compared with 6.7% of the participants in the nutritional counseling group ($p < 0.02$). There was a trend for more CBT participants to achieve full recovery compared with nutritional counseling (16.7% vs. 0%, $p < 0.097$). The second study compared CBT and maintenance treatment as usual in a sample of 88 patients with AN in a nonrandomized clinical trial (Carter et al., 2009). Within maintenance treatment as usual, participants were encouraged to seek follow-up care, with the most common option chosen by patients being individual psychotherapy and an aftercare group provided by the study's authors. Only 2.9% of the patients receiving maintenance treatment as usual received no treatment at all. At the 1-year follow-up, 26 of 46 CBT patients had completed

the full year of CBT treatment compared to 30 of 42 patients receiving maintenance treatment as usual. Relapse was operationalized in two ways: (a) BMI ≤ 17.5 for three consecutive months and (b) an average of two or more episodes per week of bingeing and/or purging for 3 months. By the 1-year follow-up, 65% of the CBT group and 34% of the group receiving maintenance treatment as usual had avoided relapse.

Touyz and colleagues (2013) conducted a study comparing CBT for AN with SSCM for 63 individuals with severe and enduring AN, which was defined as having at least a 7-year illness history of AN. This was a multisite RCT of 30 outpatient visits spread over 8 months in which individuals received either CBT for AN or SSCM, both modified for severe and enduring AN. Participants were assessed at baseline, at the end of treatment, and at 6- and 12-month post-treatment follow-ups. The focus of this study was to improve engagement in treatment and quality of life; primary outcome measures assessed quality of life, mood, and social adjustment. Weight and eating disorder psychopathology were secondary outcomes.

The study achieved a remarkable retention rate of 85% by the end of the study, and both groups showed significant and comparable improvements. The CBT for AN group had higher scores on the Weissman Social Adjustment Scale ($p = 0.038$) at the 6-month follow-up. At 12 months, the CBT group had lower EDE global scores ($p = 0.004$) and higher readiness for recovery ($p = 0.013$) compared to the SSCM group.

Clinical Implications

Taken together, this review of treatment research in AN suggests that adolescent patients can do well in psychotherapy, while adults do not fare nearly as well. Adolescents are typically ill for a shorter duration than adults with AN, and many adults have had multiple treatment series. It is hypothesized, although not yet confirmed, that there may be some fundamental difference between those who respond to early intervention efforts and those who do not, and this may help explain the relative success of some treatment modalities that focus on adolescents. In this group of young, shorter-duration cases, FBT should be considered. Family interventions that directly address the eating disorder should be offered to children and adolescents with AN according to National Institute for Clinical Excellence (NICE) guidelines. Among adults, there is no clear psychotherapy of choice that appears to be most helpful in acute care, although treatment does provide significant improvements over baseline functioning. In the case of relapse prevention, there is limited evidence supporting CBT. Finally, at the current time, pharmacotherapy does not seem to be indicated for the specific treatment of eating disorder symptoms such as low weight and overvaluation of shape and weight. There are many ongoing RCTs for AN (see Watson & Bulik, 2012, for a description) that explore both pharmacological and innovative psychotherapeutic approaches, such as cognitive remediation therapy and exposure therapy, and it is likely these will yield important information to further improve upon treatment response in both adolescent and adult patients.

TREATMENT OF BULIMIA NERVOSA

Pharmacotherapy

Many types of antidepressant medications have been studied in the treatment of BN, including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs). In a meta-analysis of nine double-blind, placebo-controlled trials of antidepressant medication, Whittal and colleagues (1999) examined 870 patients on four outcome measures: frequency of binge eating, frequency of purging, depression, and "eating attitudes" (concerns about shape and weight, self-reported dietary restraint). The overall effect sizes were 0.66 for binge eating, 0.39 for purging, 0.73 for depression, and 0.71 for eating attitudes. A review of RCTs comparing MAOIs, TCAs, and SSRIs to placebo concluded that all three of these types of medication were superior to placebo in reducing binge eating (Flament, Bissada, & Spettigue, 2012). There have been no head-to-head comparisons of different classes of drugs within a single study. However, given that both MAOIs and TCAs have a number of unpleasant side effects, and the potential for fatal overdose, they are not recommended as a first-line treatment for BN.

Of the SSRIs, fluoxetine has been the most studied in BN. The Fluoxetine Bulimia Nervosa Collaborative Study Group (1992) compared 60 mg/day with 20 mg/day with placebo in 387 women with BN for

8 weeks. The 60-mg dose was superior to placebo in reducing both binge eating (67% vs. 33%) and vomiting (56% vs. 5%). The 20-mg dose had an intermediate effect, with median reductions in binge eating and vomiting at 45% and 29%, respectively. The 60-mg dosage of fluoxetine was also associated with reduced depression and improved eating attitudes. In comparing 60 mg of fluoxetine to placebo over a 16-week period, Goldstein and colleagues (1995) found similar results regarding reductions in bingeing and vomiting. Given these data, 60 mg of fluoxetine is generally viewed as the medication treatment and dosage of choice for patients with BN.

Dropout rates are high in trials of longer-term medication use (Romano, Halmi, Sarkar, Koke, & Lee, 2002; Walsh et al., 1991). Furthermore, the long-term efficacy of antidepressant medications in BN is relatively unknown and the optimal length of treatment with medication is also unknown. Importantly, the use of bupropion is contraindicated in the treatment of BN due to an increased risk of seizures in this population (Horne et al., 1988).

The NICE (2004) guidelines provide treatment recommendations for numerous mental health conditions. These guidelines are based upon a standardized evaluation of the research evidence, and treatment recommendations are graded from A (support derived from RCTs) to C (support derived from expert opinion). The NICE guidelines rated the level of empirical support for antidepressant medication in BN as B, meaning that support is derived from well-conducted clinical studies but not necessarily RCTs.

Psychotherapy

CBT for BN has been manualized by Fairburn, Marcus, and Wilson (1993b) and targets bingeing, purging, dietary restriction, and overvaluation of weight and shape through various structured cognitive and behavioral interventions such as self-monitoring, stimulus control, and establishing regular eating patterns. The most recent meta-analysis examining the efficacy of psychological treatments for BN included 26 studies using CBT, with a total of 460 patients (Whittal, Agras, & Gould, 1999). CBT was compared to no treatment, delayed treatment, or another active psychotherapy. Seventeen of these trials reported outcomes related to binge frequency, and the effect size was 1.28. Twenty-four trials reported purge frequency outcomes with an effect size of 1.22, 19 reported depression outcomes with an effect size of 1.31, and 15 trials reported on improvements of eating attitudes with an effect size of 1.35. The authors also determined that CBT was superior to medication on each of these four outcomes.

A Cochrane Library review of psychotherapy outcomes for BN (Hay, Bacaltchuk, Stefano, & Kashyap, 2009) examined 31 controlled studies of BN. In 18 of these studies, participants were only of the purging subtype of BN, and in 3 studies participants were non-purging subtype only. This review examined binge eating and depression outcomes in studies comparing CBT to no treatment, delayed treatment, another active psychotherapy, or guided and pure self-help forms of CBT. CBT was found to be superior to delayed treatment and other psychotherapies with regards to binge eating remission. CBT was also significantly superior to delayed treatment with regards to reductions in binge eating, and it approached statistical significance in comparison to other active psychotherapy comparators. CBT approached statistical significance compared to other psychotherapies in demonstrating reductions in depression. This Cochrane Library review is a rigorous, systematic evaluation of the research; however, it is notable that data on purging and eating attitudes were not analyzed or reported.

In a recent study researchers were able to determine that CBT was more effective than psychoanalytic psychotherapy in reducing bingeing, purging, and eating-disordered cognitions even though CBT patients were treated for far fewer sessions over a much shorter period of time (Poulsen et al., 2014). Specifically, patients in the CBT condition received 20 sessions of treatment over the course of 5 months, while patients in the psychoanalytic psychotherapy condition attended an average of 72 sessions of treatment over the course of 2 years. All patients were assessed twice: at 5 months and at 2 years. After 5 months, 42% of the CBT patients were abstinent from bingeing and purging, compared with 6% in the psychoanalytic psychotherapy condition, and CBT patients had significantly lower levels of depression, eating-disordered cognitions, and interpersonal problems compared to those receiving psychoanalytic psychotherapy. At 2 years, 44% of the CBT patients were abstinent from bingeing and purging, compared with 15% in the psychoanalytic psychotherapy condition, although those in the psychoanalytic psychotherapy

condition had now experienced improvements in depression, eating-disordered cognitions, and interpersonal problems on par with those in the CBT condition. Overall, the results indicated that CBT was significantly more effective in reducing bulimic symptomatology, and it was able to achieve these results fairly quickly. These results are even more striking given the large difference in quantity and duration of treatment between the two treatment conditions.

Overall, CBT has been demonstrated to completely eliminate binge eating and purging in 30% to 50% of cases. Many other patients experience significant improvement of symptoms, and these results are often sustained long term. Furthermore, there is evidence that dietary restraint, eating, weight, and shape concerns all improve significantly over the course of treatment and in long-term follow-up, with nearly three quarters of patients demonstrating EDE global scores within one standard deviation of community norms at a 5.8-year follow-up (Fairburn et al., 1995). The NICE guidelines have given CBT a grade of A for the treatment of adults with BN, and it is the treatment of choice for this condition.

More recently, CBT for BN has been elaborated to address additional potential perpetuating factors of the eating disorder, such as low self-esteem, perfectionism, and interpersonal problems. This version of CBT is called CBT-Enhanced (Fairburn et al., 2003). There are good indications that CBT-Enhanced works well in transdiagnostic groups of participants with eating disorders, but it does not appear to be superior to CBT (Fairburn et al., 2009). As such, it appears that the active components of the treatment may be those core modules that address the eating disorder in a more focused way.

Interpersonal Psychotherapy

IPT was originally developed as a treatment for depression (Klerman, Weissman, Rounsaville, & Chevron, 1984). It is brief and time-limited and focuses on improvements in interpersonal functioning, which is known to be problematic in individuals with eating disorders (Wilfley, Stein, & Welch, 2005). Notably, IPT need not address the eating disorder, although it can be focused such that interpersonal problems are specifically linked to the maintenance of the eating disorder (Tanofsky-Kraff & Wilfley, 2010). In controlled trials comparing IPT to CBT, CBT has been found to be superior to IPT in reducing bulimic symptoms at posttreatment (Agras et al., 2000; Fairburn et al., 1991). However, at follow-up time points 1 year and 6 years later, efficacy rates do not significantly differ between the two treatments (Agras et al., 2000; Fairburn et al., 1993a, 1995). Specifically, in follow-up reports from a trial comparing CBT, IPT, and behavior therapy, 1-year remission rates of bingeing and purging were 36%, 44%, and 20%, respectively (Fairburn et al., 1993a). By the 5.8-year follow-up, remission rates were 63%, 72%, and 14%, respectively (Fairburn et al., 1995). In a large, multisite trial comparing CBT and IPT for BN (n = 220), remission rates in those completing treatment were 45% and 8% at posttreatment, with CBT being superior (Agras et al., 2000). At the 12-month follow-up, remission rates among completers were 40% in CBT and 27% in IPT, which was not a statistically significant difference. The NICE (2004) guidelines give IPT for BN the treatment recommendation of B. These guidelines note that IPT may be considered as an alternative treatment to CBT; however, the time to full improvement is significantly longer than that of CBT (approximately 8 to 12 months).

Guided Self-Help and Pure Self-Help Approaches

Pure self-help is typically in the form of a treatment book or CD-ROM given to a patient, with minimal guidance or interaction with a clinician. Guided self-help typically involves a treatment book or CD-ROM in conjunction with brief meetings with a therapist who helps the patient implement the treatment. At present the majority of studies examining self-help approaches have compared its efficacy with a waitlist control group in open trials (Sysko & Walsh, 2008). Compared to waitlist control, self-help approaches are associated with significantly greater improvement in bulimic symptoms (Bara-Carril et al., 2004; Bell & Newns, 2002; Cooper, Coker, & Fleming, 1996; Pritchard, Bergin, & Wade, 2004; Schmidt, Tiller, & Treasure, 1993). In these open trials, remission rates from binge eating ranged from 12.8% to 47%, while remission rates from purging ranged from 27% to 65.2%. Remission rates from both binge eating and vomiting ranged from 26.8% to 50%. In comparison to other active treatments, studies have been few, results have been inconsistent, and

there is evidence to suggest that self-help is less potent than in-person treatment (see Sysko & Walsh, 2008). Evidence-based self-help approaches as a first step in the treatment of BN have received a grade of B from the NICE guidelines (2004).

Clinical Implications

Taken together, the research suggests that CBT should be considered the treatment of choice in BN because it appears to be the most efficacious treatment with the quickest rate of response and the most enduring effect. However, RCTs examining IPT and antidepressants also show significant therapeutic benefit, although they do not have the same speed of impact on symptoms and endurance of treatment response as CBT. Therefore, if competent CBT clinicians are not available, or if CBT does not produce meaningful improvement, IPT and/or antidepressant medication should be considered. Finally, if individual therapy or antidepressants are not available, self-help approaches may be recommended as a first step.

TREATMENT OF BINGE EATING DISORDER

Pharmacotherapy

Weight Loss Medication

Three drugs are currently approved by the U.S. Food and Drug Administration for treating obesity: orlistat, lorcaserin, and phentermine-topiramate. Of these, only orlistat (a lipase inhibitor) has been studied as a treatment for obese individuals with BED, although topiramate (without phentermine) has also been examined. In a 24-week RCT comparing orlistat plus a low-calorie diet to placebo plus a low-calorie diet, Golay and colleagues (2005) found no significant differences between the two treatment arms with regards to reductions in binge eating; however, participants taking orlistat did lose significantly more weight than those in the placebo condition. Grilo, Masheb, and Salant (2005a) compared CBT with guided self-help plus either orlistat or placebo over 12 weeks and at a 3-month follow-up. Intent-to-treat analysis showed that binge remission rates (no binges in the past 28 days) were significantly higher at posttreatment in the group receiving orlistat (64% vs. 36%); however, by the 3-month follow-up there were no significant differences between the treatment arms, with both groups demonstrating a 52% binge remission rate. More recently, Grilo and White (2013) examined behavioral weight loss treatment plus either orlistat or placebo in an obese sample of Spanish-speaking adults. Forty participants were diagnosed with BED and 39 were not. Results for the subset of patients with BED showed that, following 4 months of treatment, binge remission rates did not differ significantly between the treatment groups (60% in the group receiving behavioral weight loss treatment and orlistat, 70% in the group receiving behavioral weight loss treatment plus placebo), nor did the groups differ on reductions in eating disorder psychopathology, depression, or BMI. At the 6-month follow-up, both treatment groups had binge remission rates of 50%.

The anticonvulsant topiramate has been examined in individuals with BED in three trials (Claudino et al., 2007; McElroy et al., 2003, 2007b). In the first of these studies, patients at a single site were randomized to receive either topiramate or placebo for 14 weeks (McElroy et al., 2003). Intent-to-treat analysis showed a binge eating remission rate of 64% in the topiramate group versus 30% in the placebo group. Individuals in the topiramate group also lost significantly more weight than those in the placebo group (5.9 kg vs. 1.2 kg, respectively). McElroy and colleagues (2007b) then conducted a large multisite RCT in which 195 patients with BED received topiramate and 199 received placebo for 16 weeks. At the end of treatment, 58% of patients on topiramate and 29% of patients on placebo attained remission from binge eating. Individuals on topiramate also lost significantly more weight than those on placebo. Finally, Claudino and colleagues (2007) compared topiramate plus CBT versus placebo plus CBT in a 21-week trial. In this sample, 37 patients were in the group receiving topiramate and 36 were in the placebo group. In intent-to-treat analysis, the binge eating remission rate was 83.8% in the topiramate group compared with 61.1% in the group receiving placebo.

Antidepressant Medication

In a 2008 meta-analysis of the effects of antidepressants in BED, Stefano and colleagues analyzed seven studies in which either TCAs (imipramine) or SSRIs (fluoxetine, fluvoxamine, sertraline, citalopram) were

used for short-term treatment (6 to 16 weeks) either in conjunction with psychotherapy or alone. Overall, binge remission rates were significantly higher at the end of treatment in the active medication treatments versus placebo (40.50% vs. 22.22%). However, these periods of treatment were relatively short (average of 8 weeks), and the study with the longest duration (16 weeks; Grilo et al., 2005b) did not find a significant difference between fluoxetine and placebo groups. Furthermore, there were no significant differences in weight change between active antidepressant medication and placebo groups.

Other Medications

Atomoxetine is a selective norepinephrine reuptake inhibitor that is FDA approved for the treatment of ADHD. McElroy and colleagues (2007a) compared atomoxetine to placebo in a 10-week RCT of adults with BED. Intent-to-treat analysis revealed that 70% of participants in the atomoxetine treatment arm achieved binge remission compared to 32% in the placebo condition. Mean weight loss in the group receiving atomoxetine was 2.7 kg compared to 0 kg in the placebo group.

Psychotherapy

Cognitive-Behavioral Therapy

There is a strong body of evidence supporting the use of CBT in the treatment of BED. CBT has been shown to be effective in significantly reducing binge eating and general eating psychopathology both directly following treatment and after longer-term follow-up. CBT produces higher binge abstinence rates than no treatment and behavioral weight loss treatment (Grilo & Masheb, 2005; Munsch et al., 2007; Schlup et al., 2009). Grilo and colleagues (2011) compared (a) 16 sessions of CBT with (b) 16 sessions of behavioral weight loss treatment and (c) 16 sessions of CBT followed by 16 sessions of behavioral weight loss treatment in an RCT of 125 obese individuals with BED. CBT was superior to behavioral weight loss treatment with regards to binge eating abstinence at posttreatment and continuing through a 12-month follow-up (51% in the CBT group, 36% in the behavioral weight loss treatment group, and 40% in the combined treatment group). While behavioral weight loss treatment produced significantly greater reductions in BMI by posttreatment, there were no significant group differences in weight loss by the 12-month follow-up. CBT also appears to be superior to pharmacological treatment of BED. In a 12-month follow-up of an RCT of obese binge eaters, Grilo and colleagues (2012) found that adding fluoxetine to CBT treatment did not add significantly to the efficacy of CBT on its own.

Less intensive guided self-help versions of CBT have also been examined in the treatment of BED. An early, small RCT (Loeb, Wilson, Gilbert, & Labouvie, 2000) compared guided and unguided CBT self-help conditions in an adult binge eating sample and showed an advantage for therapist guidance. Wilson and colleagues (2010) conducted an RCT of 205 overweight and obese individuals with BED who were randomized to either 20 sessions of behavioral weight loss treatment or IPT or 10 sessions of guided CBT self-help over the course of 6 months. At a 2-year follow-up, both IPT and guided CBT self-help were shown to produce significantly higher rates of binge remission (65% and 67% respectively) compared to behavioral weight loss treatmen (47%). The efficacy of IPT and guided CBT self-help did not differ significantly, although guided CBT self-help was less effective than IPT among patients with low self-esteem and high eating pathology scores as measured by the EDE. In a study of binge eating within a primary care sample, Striegel-Moore and colleagues (2010) compared guided CBT self-help to treatment as usual. Eighty-nine percent of this sample had either full or subclinical BED, while the remaining 11% had been diagnosed with BN. At the 12-month follow-up, CBT was associated with higher binge abstinence rates than treatment as usual (64% vs. 45%) and greater reductions in eating disorder pathology.

Interestingly, while CBT has been shown to be superior to IPT in the treatment of BN, the two treatments appear to be equally efficacious in the treatment of BED. In a large RCT comparing CBT with IPT in the treatment of adults with BED, binge eating abstinence rates were 79% and 73%, respectively, at posttreatment and 59% and 62% at a 1-year follow-up (Wilfley et al., 2002). At the 4-year follow-up there were still no significant differences between the groups (Hilbert et al., 2012). Although there have been fewer studies of treatment of BED using IPT as compared to CBT, the existing evidence does suggest it is efficacious.

Behavioral Weight Loss

Behavioral weight loss has been studied as a nonspecialist treatment for BED. As noted above, results indicate that individuals receiving behavioral weight loss treatment achieve binge abstinence at a significantly lower rate than specialist BED treatments such as CBT and IPT (Grilo et al., 2011; Wilson et al., 2010). In addition to the studies previously discussed in this chapter, Devlin and colleagues (2005) compared 20 sessions of (a) behavioral weight loss treatment plus CBT and either fluoxetine or placebo with (b) behavioral weight loss treatment with fluoxetine or placebo. All iterations of treatment involving CBT had significantly higher binge remission rates (62%) than those involving behavioral weight loss treatment with only fluoxetine or placebo (33%). This pattern of results was maintained at the 2-year follow-up (Devlin et al., 2007).

Dialectical Behavior Therapy

Dialectical Behavior Therapy (DBT), which has shown to be a well-validated and effective treatment for those with impaired emotion regulation, has been adapted for BED (Linehan, 1993). At present there are few RCTs comparing DBT for BED to either waitlist control or other active treatments. However, the results of the few trials that have been done suggest that it is worthy of further investigation. A trial comparing DBT to waitlist demonstrated that DBT led to a significantly greater reduction in eating pathology and binge eating (Telch, Agras, & Linehan, 2001). More recently, DBT was compared to an active comparison group therapy in 101 adults with BED over the course of 20 group sessions (Safer, Robinson, & Jo, 2010). At posttreatment, significantly more patients in the DBT group had attained binge remission (64%) compared to active comparison group therapy (36%). By the 12-month follow-up these group differences had disappeared, with abstinence rates being 64% vs. 56%, respectively.

CONCLUSIONS

Eating disorders, particularly AN, have been notoriously challenging to treat. The psychological and pharmacological intervention outcome literature emerging over the past 20 years or so reviewed here provides valuable research data to inform best clinical practices; this body of literature also highlights the need for multiple areas of further study. Specifically, for AN, while promising treatment strategies exist for children and adolescents, there is a dearth of significant findings to guide intervention for acute care for low-weight adults with AN. CBT shows promise in terms of relapse prevention for those adults who respond to earlier treatment interventions that focus on weight gain and stabilization. Retention challenges among adult studies compromise both research and clinical efforts to alleviate suffering in this pernicious disorder. In BN, CBT is the clear treatment of choice for achieving rapid and sustained benefits, with additional interventions (IPT and pharmacotherapy) as viable alternatives; however, there is significant room for improvement in terms of achieving full remission, the optimal outcome for any psychiatric disorder. For BED, psychological, behavioral, and pharmacological treatment modalities, and many specific interventions within each of these categories, result in significant reductions in binge eating. In contrast, weight loss, an additional treatment goal in this often overweight or obese patient population, is rarely seen as a secondary benefit. Given the number of efficacy trials under way for AN, the next two decades are likely to bring more information to shape effective clinical practice in eating disorders, informed by the advances in risk factors research to guide prevention strategies.

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21

Treatment of Sleep Disorders

Deepa Burman
Daniel J. Buysse
Charles F. Reynolds, III

This chapter provides an evidence-based review of the seven categories of *DSM-5* sleep-wake disorders. Specific sleep-wake disorders vary widely in their clinical manifestations, etiologies, treatment, and the level of evidence supporting those treatments. Sleep-wake disorders are prevalent, increase the risk of many common mental and substance use disorders, and exacerbate these disorders, with which they typically co-occur. Unless properly treated in their own right, sleep-wake disorders can impair treatment response and worsen the long-term course of mental disorders. Thus, it is important for psychiatrists and other mental health practitioners to understand the diagnosis and treatment of sleep-wake disorders and when to refer the patient for consultation with a sleep medicine specialist.

INTRODUCTION

Traditionally, psychiatrists have considered sleep disorders/problems to be symptoms of psychiatric disorders. Chronic sleep problems affect 50% to 80% of patients in a typical psychiatric practice, compared with 10% to 18% of adults in the general U.S. population. Similarly psychiatric morbidity is high in patients seen in the sleep disorders clinic. In reality, the relationship between sleep and psychiatric disorders is found to be bidirectional, such that each can amplify the disability and suffering of the other. Moreover, sleep disturbances such as insomnia disorder are potent risk factors for the onset of common mental disorders. For example, Baglioni and colleagues (2011) found that nondepressed people with insomnia have a twofold risk of developing depression (Roth et al., 2006).

Understanding sleep disorders is thus critical for the management of psychiatric patients. According to the *DSM-5* classification of sleep-wake disorders there are 10 disorder groups: insomnia disorder, hypersomnolence disorder, narcolepsy, breathing-related sleep disorders, circadian rhythm sleep-wake disorders, non–rapid-eye-movement (NREM) sleep arousal disorders, nightmare disorder, rapid eye movement sleep behavior disorder, restless legs syndrome, and substance/medication-induced sleep disorder. Impairment of daytime function is a critical feature of all these disorders. The goal of this chapter is to review evidence-based treatment for *DSM-5*-defined sleep-wake disorders and to provide guidance to the nonspecialist about when to consider referral to a sleep specialist for further assessment and management of patients. In each section below, we provide citations to clinically useful reviews of treatment. Further details on the features and pathophysiology of individual sleep disorders can be found in other sources such as "Clinical Pharmacology of Other Drugs Used as Hypnotics" by Buysse and colleagues (2010), in Principles and Practice of Sleep Medicine, edited by Kryger and colleagues.

INSOMNIA DISORDER

Overview and Diagnosis

Insomnia is a significant health problem because of its high prevalence, treatment challenges, and high socioeconomic burden. It is characterized by difficulty in falling or staying asleep or returning to sleep after a middle-of-the-night awakening. An essential feature of insomnia disorder is dissatisfaction with sleep quality or quantity. It is the most prevalent of all sleep disorders, with a higher female preponderance compared to males. *DSM-5* consolidated various insomnia disorders from *DSM-IV* into a single diagnosis because of the difficulty in discriminating "primary" and "secondary" forms and the reality of high comorbidity. To warrant an insomnia disorder diagnosis, the sleep difficulty should occur at least 3 nights a week for at least 3 months despite adequate opportunity for sleep. This distinguishes it from sleep deprivation. Nonrestorative sleep is no longer a feature of insomnia in *DSM-5*.

A detailed and careful 24-hour sleep-wake history is crucial for the diagnosis and management of insomnia disorder. Evaluation using a 1- or 2-week sleep-wake diary should be considered whenever possible. An example of a sleep-wake diary can be seen in Figure 21.1. Polysomnography is not usually indicated for insomnia disorder unless there is concern about other coexisting sleep disorders based on history.

Patients should be reassessed every few weeks or monthly until symptoms are stable or have resolved. Because of the high relapse rate, regular follow-ups every 6 months or annually should be considered. "Sleep hygiene" measures should be combined with other forms of insomnia treatment, but sleep hygiene alone has not been found to be effective for treatment of chronic insomnia.

Management

Insomnia treatments aim to improve the amount and quality of sleep and also to enhance daytime function. Ideally, short-term pharmacological treatment should be supplemented with behavioral and cognitive strategies. Whenever medications are prescribed, treatment goals and expectations should be discussed along with safety, side effects, potential for dose escalation, and rebound insomnia. Long-term medication treatment should be accompanied by consistent follow-up and ongoing monitoring for efficacy, side effects, and newly developed comorbid conditions.

Psychological and Behavioral Treatments

Psychological and behavioral treatments for insomnia have been evaluated in many randomized controlled trials (RCTs) and meta-analyses. In general, these treatments aim to reduce sleep latency and improve sleep consolidation by changing behaviors, habits, and cognitions that interfere with sleep. The best evidence for efficacy among the various approaches is for multicomponent cognitive-behavioral treatment of insomnia (CBT-I), stimulus control therapy, and sleep restriction therapy. Behavioral approaches are comparable to medications in efficacy and are found to be more durable. Currently there is insufficient evidence to recommend sleep hygiene education, imagery training, or cognitive therapy as monotherapies.

Table 21.1 summarizes the major components of behavioral and psychological treatments for insomnia that can be administered individually or in a group.

CBT-I combines cognitive therapy with behavioral techniques and is typically delivered over six to eight individual treatments. It relies on the patient being an active participant in his or her own treatment. The behavioral component may include stimulus control therapy and/or sleep restriction therapy with or without use of relaxation therapy. Cognitive therapy aims at changing the patient's beliefs and attitudes about insomnia. It uses a psychotherapeutic method to reconstruct cognitive pathways with positive and appropriate concepts about sleep and its effects (Hauri, 1991b; Jacobs, Pace-Schott, Stickgold, & Otto, 2004; Spielman, Saskin, & Thorpy, 1987).

Cognitive-behavioral approaches use sleep diaries for assessment and monitoring of treatment outcomes. They require patients to work on bedtimes and wake times, thereby using voluntary waking behaviors to influence sleep. The generic applicability of the behavioral/psychological approaches rests with their basis in the two-process model of sleep regulation along with an understanding that stimulus-linked conditions or sleep-related beliefs that foster wakefulness are often good targets for modification. Substantial data support the process of sleep propensity being normally governed by the length of time a person is

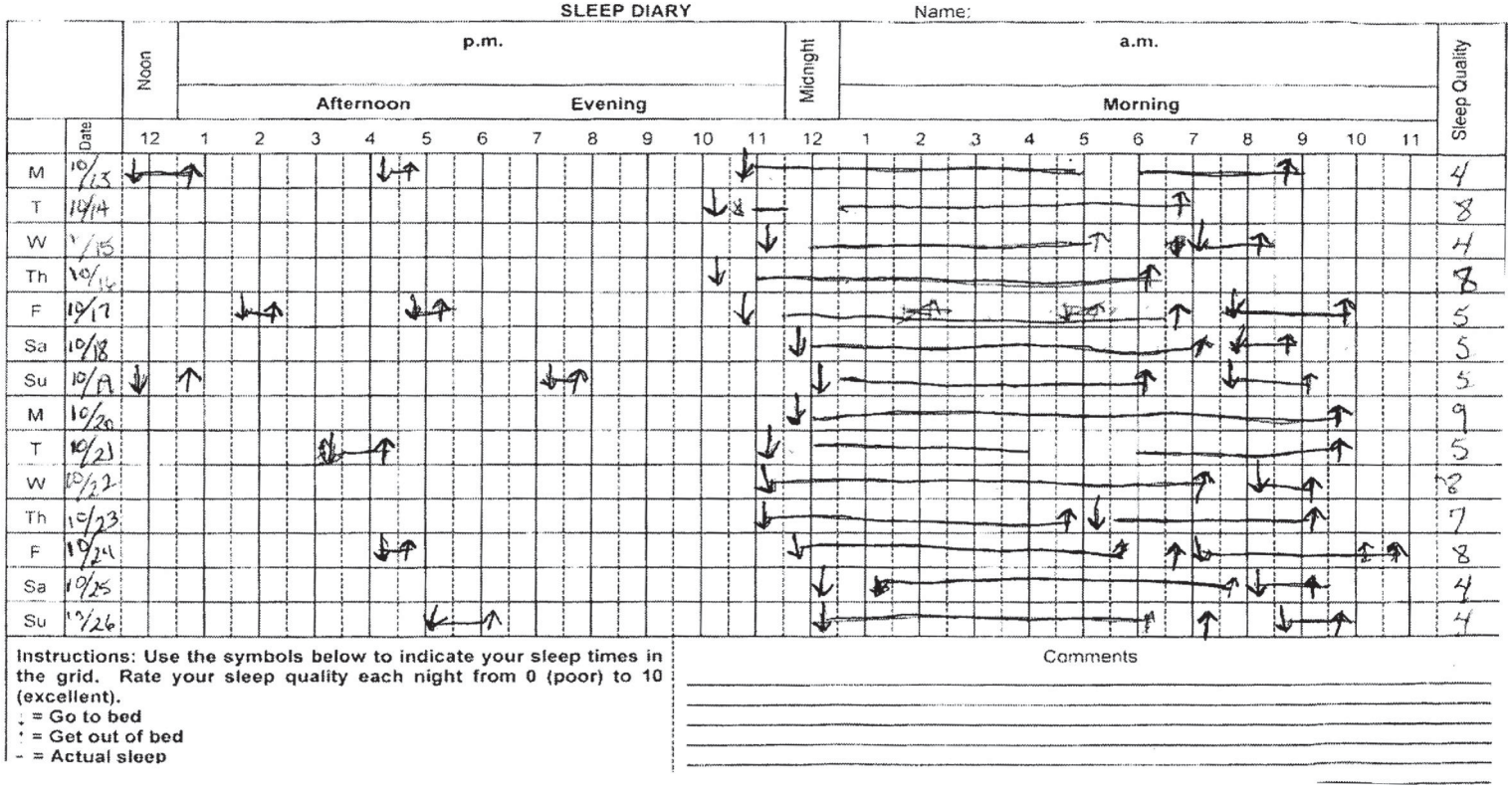

FIGURE 21.1 Sleep diary. A sleep diary (log) is a visual record designed to gather information about a patient's sleep patterns. It should be completed within an hour of getting out of bed, and the best estimate of sleep wake timing should be recorded. (Adapted from the American Academy of Sleep Medicine.)

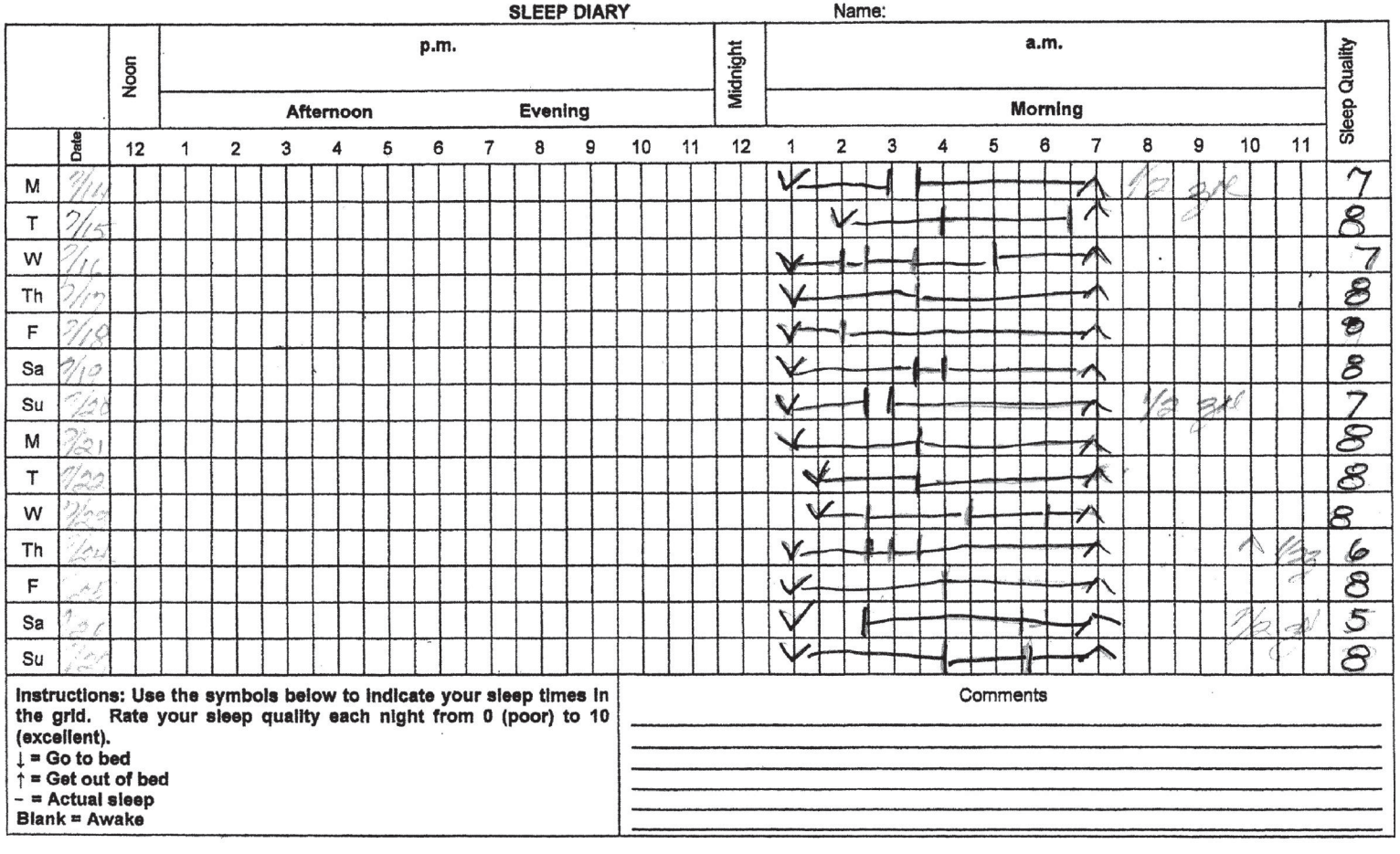

FIGURE 21.1 Continued

TABLE 21.1 Psychosocial Treatments of Insomnia

Type of Treatment	*Description*	*Key Elements*	*Evidence for Efficacy*	*Evidence Grade*	*Key References*
CBT-I	Multimodal treatment that combines cognitive therapy with behavioral interventions.	Sleep education Stimulus control techniques Sleep restriction techniques Cognitive therapy techniques May include relaxation training.	Based on various meta-analyses, systematic review, and clinical trials. The findings indicate that nonpharmacological therapies produce reliable and durable changes in several sleep parameters of chronic insomnia patients. The data indicate that between 70% and 80% of patients treated with nonpharmacological interventions benefit from treatment.	Type 1 & 2 studies	Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012 C. M. Morin, Culbert, & Schwartz, 1994 Montgomery & Dennis, 2003 Morin et al., 2006 Okajima, Komada, & Inoue, 2011
Stimulus control	Based on operant and classical conditioning principles: nonsleep activities and the bedroom environment can serve as stimuli that interfere with sleep. Treatment prescribes behaviors that strengthen associations between the environment and sleep.	Go to bed only when sleepy. Use the bed and bedroom for sleep only. Do not read, watch television, talk on the phone, worry, or plan activities in the bedroom. If unable to fall asleep within 10–20 min, leave the bed and the bedroom. Return only when feeling sleepy again. Set the alarm and wake up at a regular time every day. Do not use the snooze button on the alarm. Do not nap during the day.	Based on at least 2 between-group design studies demonstrating efficacy in more than one way. Stimulus control was as effective as sleep education plus relaxation and more effective than a waitlist control. Stimulus control treatment produced significant improvements on most sleep parameters relative to no additional treatment.	Type 1–3 studies	Riedel, Lichstein, & Peterson, 1998 Lacks, Bertelson, Sugerman, & Kunkel, 1983 Morin et al., 1994 Smith, Perlis, Park, & Smith, 2002 Baillargeon & Demers, 1998

(*continued*)

TABLE 21.1 (continued)

Type of Treatment	*Description*	*Key Elements*	*Evidence for Efficacy*	*Evidence Grade*	*Key References*
Relaxation techniques	Muscular tension and cognitive arousal are incompatible with sleep. Relaxation decreases waking arousal and facilitates sleep at night.	Specific techniques may include progressive muscle relaxation, guided imagery, paced breathing.	Clinical trials. Studies contrasting relaxation-based interventions to a control condition found relaxation more effective than waitlist, placebo, or no treatment. Relaxation was more effective for sleep onset.	Type 2 & 3 studies	Friedman, Bliwise, & Yesavage, 1991 Means, Lichstein, & Epperson, 2000 Lichstein, Riedel, & Wilson, 2001
Biofeedback	Three types of biofeedback have been specifically tested for the treatment of insomnia: EMG, theta EEG, and sensorimotor rhythm EEG.	Visual or auditory feedback to patients helps them control physiological parameters and reduce somatic arousal.	Very few studies with effects of biofeedback for treating insomnia. All studies available show that it is an effective modality for treatment of insomnia, but it takes longer than other forms of relaxation therapy with little appreciable advantage.	Type 3 & 6 studies	Nicassio & Boylan, 1982 Freedman & Papsdorf, 1976 VanderPlate & Eno, 1983 Cortoos, de Valck, Arns, & Breteler, 2010
Sleep restriction	Based on experimental evidence that sleep is regulated by circadian and homeostatic processes. Treatment increases homeostatic sleep drive by reducing time in bed and maintaining a consistent wake time in the morning to reinforce circadian rhythms.	Restrict time awake in bed by setting strict bedtime and rising schedules limited to the average number of hours of actual sleep reported in 1 night. Keep a fixed wake-up time, regardless of actual sleep duration. If after 10 d sleep efficiency is lower than 85%, further restrict bedtime by 15–30 min. Increase time in bed by advancing bedtime by 15–30 min when the time spent asleep is at least 85% of time in bed.	Based on clinical trials and meta-analysis. Reduction in wake time after sleep onset, increased sleep efficiency and total sleep time. Also noted to have improvement in subjective assessment.	Type 2–4 studies	Vincent, Lewycky, & Finnegan, 2008 Wohlgemuth & Edinger, 2000 Morin, Hauri, Espie, & Spielman, 1999 Spielman, Saskin, & Thorpy, 1987 Morin et al., 1994

Sleep hygiene	Recommendations promoting behaviors that help sleep, discouraging behaviors that interfere with sleep	Specific recommendations vary across studies. Typical recommendations include: Do not try to sleep if not sleepy. Avoid stimulants (caffeine, nicotine). Limit alcohol intake. Maintain a regular sleep schedule 7 nights per wk. Avoid naps. Get regular exercise at least 6 h prior to sleep. Keep the bedroom dark and quiet.	Insufficient evidence to be an option as a single therapy. Whether this therapy is effective when added to other specific approaches could not be determined from available data.	Type 2–5 studies	Jefferson, Drake, Scofield, & Myers, 2005 Stepanski & Wyatt, 2003 Schoicket, Bertelson, & Lacks, 1988 Hauri, 1991a
Cognitive therapy	Identify, challenge, and replace dysfunctional beliefs and attitudes regarding sleep and sleep loss. These beliefs increase arousal and tension, which impede sleep and further reinforce the dysfunctional beliefs.	Challenge unhelpful beliefs and fears about sleep (e.g., overestimation of numbers of hours of sleep necessary to be rested; apprehensive expectation that sleep cannot be controlled; fear of missing opportunities for sleep). Thought journaling to reduce rumination. Design behavioral "experiments" to test beliefs about sleep.	Ongoing research to be an option as a single therapy. Extensive evidence for effectiveness when used with other therapies.	Type 3 studies	Belanger, Savard, & Morin, 2006 Harvey, 2002 Harvey et al., 2007 Okajima et al., 2011 Yook, Lee, Ryu, Kim, & Choi, 2008

continuously (i.e., not napping) awake ("Process S") *and* by the biological time of day as set by the suprachiasmatic nuclei of the hypothalamus governing the body's circadian rhythms ("Process C"). It is Process C that makes it more difficult to remain awake between 3 and 5 a.m. (Fig. 21.2).

Based on these principles, CBT-I includes restricting time in bed to match actual sleep time, setting a regular sleep-wake time regardless of the duration of sleep the night before. New treatment modalities are being investigated to disseminate these treatments and reduce patient burden and costs; they include home-based treatment (Espie, Inglis, Tessier, & Harvey, 2001), telephone interventions, Internet-based interventions (Morin, Stone, Trinkle, Mercer, & Remsberg, 1993), and self-help material (Mimeault & Morin, 1999).

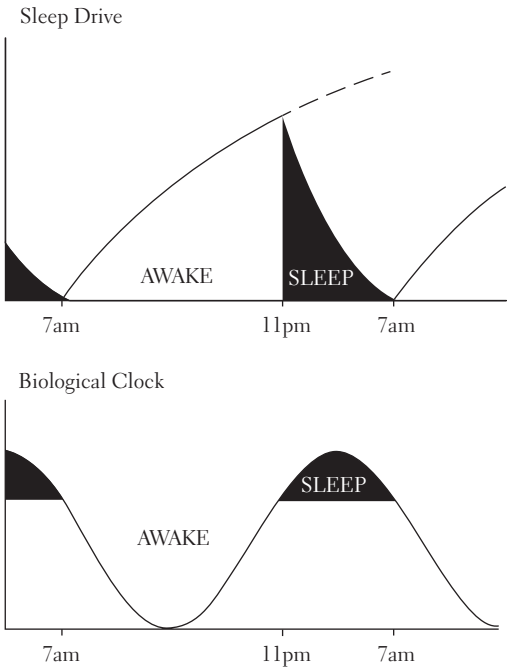

FIGURE 21.2 The two-process model. Alertness level is determined by the interaction between two regulatory processes. The sleep homeostatic drive (Process S) promotes sleep and builds up during extended wakefulness, reaching a maximum in the late evening (near the usual sleep time). The circadian rhythm system (Process C) promotes wakefulness during the day. It is biphasic and tends to dip in the midafternoon. Process C also reaches its peak in the evening to counterbalance the accumulation of homeostatic drive that has built up throughout the day, and it begins to fall just before the usual bedtime. This system promotes wakefulness during the day and consolidates sleep at night (Borbely, 1982).

Pharmacological Treatments

Hypnotic therapy should be considered for insomnia when the patient is significantly distressed by disturbed sleep, when the sleep disturbance is deleterious to the patient's overall safety or health, when cognitive-behavioral approaches are unavailable or unsuccessful, or when the patient is unwilling or unable to engage in CBT. Benzodiazepine receptor agonists are the mainstay of pharmacological treatment for insomnia, although many agents other than benzodiazepine receptor agonists are also used in the treatment of insomnia; these include agents classified as antidepressants, antipsychotics, antihistamines, anticonvulsants, melatonin agonists, and herbals as well as chloral hydrate and sodium oxybate (Bertisch, Herzig, Winkelman, & Buettner, 2014).

Among the many medications used to treat insomnia, a much smaller number are approved by the U.S. Food and Drug Administration (FDA) for this indication. Currently approved drugs include benzodiazepine receptor agonists, one tricyclic drug, one melatonin receptor agonist, antihistamines, barbiturates (Krystal, 2009; Walsh 2004) and an orexin receptor antagonist.

Table 21.2 summarizes various pharmacological treatment methods for insomnia and Table 21.3 summarizes herbal and over-the-counter treatments.

There is considerable evidence indicating that the benzodiazepine receptor agonists are efficacious in the treatment of insomnia, whether primary or comorbid, chronic or transient. They have a wide margin of safety as commonly used in clinical practice. Meta-analyses have demonstrated the they are efficacious in the treatment of chronic insomnia (Holbrook, Crowther, Lotter, & Endeshaw, 2001; Soldatos, Dikeos, & Whitehead, 1999) on self-reported outcomes of sleep latency, sleep duration, number of awakenings, and sleep quality. Effects are comparable in magnitude to those of CBT (Smith, Fogg, & Eastman, 2009).

The 2005 National Institutes of Health state-of-the-science report on the management of chronic insomnia concluded that the benzodiazepine receptor agonists are the only medications with an established

TABLE 21.2 Pharmacological Treatments

Medications	*Key Clinical Points*	*Main Side Effects*	*Relative Contraindications*	*Evidence for Efficacy*	*Evidence Grade*	*Key References*
Benzodiazepine receptor agonists (nonbenzodiazepines)	First-line hypnotics. Margin of safety or therapeutic index is wide.	Sedation, anterograde amnesia, ataxia, sleep walking, sleep violence or sleep related eating disorders, respiratory depression. Rebound insomnia, tolerance and abuse may occur.	Concomitant illnesses such as obstructive sleep apnea, substance use disorder, or advanced liver disease.	RCTs of benzodiazepine receptor agonist hypnotics Adults younger than 65 years N = 1894 Moderate effect sizes (d = 0.56–0.71) for self-reported outcomes of sleep latency, total sleep time, number of awakenings, sleep quality Z scores for effect sizes range from 0.71 to 0.76	Type 1 studies	Buysse, 2013 Roehrs & Roth, 2012 Schutte-Rodin, Broch, & Buysse, 2008 Riemann & Perlis, 2009 Walsh & Roth, 2011

(*continued*)

TABLE 21.2 (continued)

Medications	*Key Clinical Points*	*Main Side Effects*	*Relative Contraindications*	*Evidence for Efficacy*	*Evidence Grade*	*Key References*
Benzodiazepines	Agonists at benzodiazepine receptor GABA-A site. Different medications have different durations of action.	Sedation, ataxia, anterograde amnesia, ataxia, sleep walking, sleep violence or sleep related eating disorders, respiratory depression. Rebound insomnia, tolerance and abuse may occur.	Concomitant illnesses such as obstructive sleep apnea, substance use disorder, or advanced liver disease.	RCTs of benzodiazepine hypnotics compared to placebo or other active treatments N = 2,672 Self-report outcomes: Significant difference favoring benzodiazepines vs. placebo for sleep latency, total sleep time Polysomnography outcomes: Significant difference favoring benzodiazepines vs. placebo for total sleep time Side effects (drowsiness, dizziness, lightheadedness): Significantly more likely in patients taking benzodiazepines vs. placebo. Reduce time to sleep onset, prolonged stage 2, prolonged total sleep time and some reduction in REM sleep.	Type 1 & 2 studies	Holbrook et al., 2001 Holbrook, Crowther, & Lotter, 2000 Nowell, Mazumdar, Buysse, & Dew, 1997

	Sedative antidepressants (e.g., doxepin, trazodone)	Sedative nature due to central anticholinergic or antihistaminergic activity. There is also possible effect of serotonin 5HT2 receptor antagonism and alpha 1 antagonism. Helpful in patients with concomitant depression. Doxepin is FDA approved for sleep maintenance insomnia.	Somnolence, headache, dizziness and nausea. Priapism is a relatively uncommon side effect of trazodone.	Hypersensitivity and use of MAO inhibitors within 14 days. Dry mouth, constipation, narrow-angle glaucoma, and urinary retention with doxepin. Trazodone to be used with caution in those at risk of falls because of orthostatic hypotension.	RCTs of benzodiazepine receptor agonists and antidepressant drugs in chronic insomnia Antidepressants: Significant effects on polysomnographic wake after sleep onset, sleep efficiency, total sleep time; and on sleep diary rating of sleep quality Adverse events significantly greater for benzodiazepine receptor agonists and antidepressants vs. placebo	Type 1–3 studies	Krystal, Lankford, Durrence, & Ludington, 2011 Richey & Krystal, 2011 Wiegand, 2008 Buscemi, Vandermeer, Friesen, & Bialy, 2007 Glass, Sproule, Herrmann, & Busto, 2008 Mendelson, 2005
	Ramelteon	First melatonin receptor agonist for treatment of insomnia	Headache, dizziness, somnolence, fatigue, nausea	History of angioedema with ramelteon and concurrent use of fluvoxamine. Use in severe liver failure.	8 placebo-controlled RCTs of ramelteon in chronic insomnia. Sleep latency reduced in patients 18–64 years old. No difference in percentage of REM on polysomnography between ramelteon and placebo. Well tolerated without major side effects. No dose–response relationship observed. No next-day residual daytime sedation.	Type 1 & 2 studies	Mayer, Wang-Weigand, & Roth-Schechter, 2009 Reynoldson & Elliott, 2008 Sateia, Kirby-Long, & Taylor, 2008 Miyamoto, 2009 Ferguson, Rajaratnam, & Dawson, 2010 Kuriyama, Honda, & Hayashino, 2014

TABLE 21.2 (continued)

Medications	*Key Clinical Points*	*Main Side Effects*	*Relative Contraindications*	*Evidence for Efficacy*	*Evidence Grade*	*Key References*
Mirtazapine	Sedating effects diminish in doses greater than 30 mg due to adrenergic effects. Antagonizes adrenergic, serotonergic and histaminergic receptors.	Increased appetite and weight gain. Dry mouth and constipation.	Used with in caution in patients with bipolar disorder, obesity, liver disease and kidney disease	Clinical trials and open-label studies. Improves sleep continuity in depressed patients with poor sleep quality. Decreased sleep latency, increased total sleep time and sleep efficiency. No effect on REM sleep.	Type 3–6 studies	Winokur et al., 2000 Wichniak, Wierzbicka, & Jernajczyk, 2012
Sedative antipsychotics: quetiapine, olanzapine	Used in doses lower than typically used in their FDA-approved indications. Antagonize dopamine, histamine, serotonin, muscarinic, cholinergic, and adrenergic receptors. Improves sleep primarily in patients with mood disorders.	Orthostatic hypotension, dizziness, dry mouth, constipation, blurred vision, urinary retention, weight gain and sedation. Can lead to extrapyramidal side effects, which are less common in newer agents. Olanzapine associated with cognitive impairment, glucose intolerance, elevated risk of mortality among patients with dementia.	Used with caution in patients with myocardial infarction, ischemia or conduction abnormalities, closed-angle glaucoma, decreased gastrointestinal motility, urinary retention, or hypotension.	Clinical studies demonstrate decrease in sleep latency, increased sleep efficiency and improved subjective sleep quality.	Type 3, 5, & 6 studies	Monti & Monti, 2004 Anderson & Griend, 2014 Wiegand et al., 2008 Wine, Sanda, & Caballero, 2009 Cohrs et al., 2004

TABLE 21.3 Over-the-Counter Medications for Insomnia

Medications	*Key Clinical Points*	*Main Side Effects*	*Evidence for Efficacy*	*Evidence Grade*	*Key References*
Melatonin	Used both as a hypnotic and as a chronobiotic to phase shift circadian rhythms. Studied in adults and children.	Daytime somnolence	Crossover studies and clinical trials, Associated with reduced sleep latency and improved quality of sleep. Less consistent effects on sleep maintenance. Dose–response effect has not been established.	Type 2, 3, 4, 5 studies	Smits, Nagtegaal, van der Heijden, Coenen, & Kerkhof, 2001 Ferracioli-Oda, Qawasmi, & Bloch, 2013
Valerian root	One of the 10 most popular herbal products sold in the United States	Hepatotoxic	Meta-analysis of 18 studies found that valerian decreased objective sleep latency by less than 1 minute compared to placebo.	Type 2, 3, 4, 5 studies	Nunes & Sousa, 2011 Sarris & Byrne, 2011 Balderer & Borbély, 1985 Fernández-San-Martín et al., 2010
Antihistamines (e.g., diphenhydramine and doxylamine)	Antagonizes H1 histamine receptors	Closed-angle glaucoma, decreased gastrointestinal motility, urinary retention, asthma, chronic obstructive pulmonary disease, and severe liver disease. There have been reports of coma and rhabdomyolysis occasionally occurring with doxylamine.	Sleep-enhancing effects of diphenhydramine noted in placebo-controlled trials of sleep disturbance in a mixed group of psychiatric patients. Effects on sleep maintenance more consistent than sleep onset. No studies with doxylamine.	Type 2, 3, 5 studies	Glass et al., 2008 Griend & Anderson, 2012 Smith & Smith, 1985

scientific basis (i.e., clearly defined risk and benefit by dose) for use for insomnia. Thus, for most patients with chronic insomnia, pharmacotherapy should be initiated with a benzodiazepine receptor agonist at the lowest effective dose for the shortest clinically necessary period of time.

Benzodiazepine receptor agonists act at a specific recognition site on the GABA-A receptor that is distinct from the actual GABA binding site. They increase the affinity for GABA binding, thereby promoting the inhibitory actions of this neurotransmitter. Significant differences in pharmacokinetic profiles exist among the benzodiazepine receptor agonists, thereby providing physicians with therapeutic options that have differing durations of action, with half-lives varying from 1 hour to greater than 100 hours. Half-life and duration of action can help to guide the clinician on the choice of a particular drug. For instance, a patient with primarily sleep-onset difficulties may benefit from a short-acting hypnotic, whereas a patient who has trouble staying asleep may benefit from a longer-acting agent (Kryger, Roth, & Dement, 2010; Mendelson, 2011).

The primary contraindications to the use of benzodiazepine receptor agonists are concomitant illnesses, such as obstructive sleep apnea, substance abuse disorder, or advanced liver disease. However, these cases represent relative rather than absolute contraindications.

Although they are generally well tolerated, benzodiazepine receptor agonists can cause adverse effects, including sedation, memory impairment, impaired balance, impaired driving performance the day after dosing, and complex sleep-related behaviors. The latter may include eating, walking, and sexual activity while ostensibly asleep. Abrupt discontinuation of benzodiazepine receptor agonists can be associated with rebound insomnia and withdrawal symptoms.

Doxepin is a tricyclic antidepressant approved as a hypnotic agent. At low doses (3 to 6 mg) it has been approved as a hypnotic. It reduces wakefulness across the night and improves sleep efficiency (Krystal et al., 2011). At hypnotic doses, doxepin has antihistamine (H1) effects and very few effects on serotonin, norepinephrine, or dopamine neurotransmission. This accounts for sedation and without some of the toxicity and side effects associated with anticholinergic properties at high doses. Although not formally approved, low-dose trazodone and mirtazapine are commonly used to treat insomnia. Melatonin and a melatonin receptor agonist, ramelteon, have been used as hypnotics, and ramelteon is FDA approved for this purpose. Both have been shown to decrease subjective sleep latency. They have fewer side effects compared to benzodiazepine receptor agonists (Buysse, Bate, & Kirkpatrick, 2005; Erman, Seiden, Zammit, Sainati, & Zhang, 2006). Antihistamines are another class of commonly used over-the-counter agents to treat insomnia. Their efficacy and side effects have not been rigorously evaluated. Most promising use has been shown in insomnia associated with allergy symptoms.

Other drugs used in the treatment of insomnia include valerian, gabapentin and pregabalin, and sedating antipsychotic drugs. Very limited evidence supports the efficacy and safety of these drugs for treating insomnia.

In 2014 the FDA approved the orexin receptor antagonist suvorexant for the treatment of insomnia, the first drug its class.

HYPERSOMNOLENCE DISORDER AND NARCOLEPSY

Overview and Diagnosis

The essential feature of hypersomnolence disorder and narcolepsy is excessive daytime sleepiness that is not due to disturbed nocturnal sleep, occurring at least three times a week for at least 3 months. In narcolepsy, irresistible sleep occurs intermittently during waking hours. In addition, the patient must have at least one of the following: cataplexy episodes, defined by brief episodes of sudden bilateral loss of muscle tone precipitated by strong emotions but preserved consciousness; hypocretin deficiency in cerebrospinal fluid; or nocturnal polysomnography findings of REM latency less than 15 minutes or mean sleep latency of less than 8 minutes with two episodes of REM sleep during a mean sleep latency test. The mean sleep latency test is the key test for diagnosis of narcolepsy, in which the patient is required to take five naps during the day. The mean time to sleep onset and the presence of REM sleep are measured. For improved validity of the mean sleep latency test, it should be interpreted in the context of the patient's clinical findings.

In hypersomnolence disorder, excessive sleepiness occurs despite a main sleep period of at least 7 hours. Nighttime sleep is of long duration with good sleep continuity but is nonrestorative.

A careful history must be obtained in all cases. Because of its importance in the diagnosis of narcolepsy, cataplexy should be assessed in detail. Possible substance abuse must be elicited as well. The Epworth Sleepiness Scale, an eight-item self-report instrument that assesses the tendency to doze in various scenarios, is commonly used to assess sleepiness in hypersomnolence disorder, narcolepsy, and other sleep disorders. The total score ranges from 0 to 24, with a score of 10 or more suggesting pathological sleepiness. Sleep logs and/or actigraphy can be helpful to rule out sleep deprivation/restriction. Narcolepsy is associated with deficiency of the peptide neurotransmitter hypocretin (orexin) and loss of orexin-containing cells in the lateral hypothalamus. Projections from the lateral hypothalamus innervate arousal centers of the brain stem and posterior hypothalamus, and loss of orexinergic cells is associated with instability of sleep-wake states. Levels of hypocretin-1 in cerebrospinal fluid can be measured; low levels are found in most cases of narcolepsy. Because of difficulty in performing lumbar punctures and the absence of routine clinical laboratories for assays, its use is reserved for complex cases.

Although driving and working can be impaired in untreated cases, once hypersomnolence disorder or narcolepsy is controlled, patients can consider driving with caution. In addition to medical and behavioral management, referral to support groups is often helpful for social support.

Management

Since no cure of hypersomnolence or narcolepsy currently exists, treatment is aimed at symptom control to allow patients to live a full personal and professional life. Treatment of hypersomnolence is very similar to that of narcolepsy. The mainstay of treatment is pharmacological, although adjunctive behavioral therapy plays a role in adapting to the situation. Treatment aims at reducing excessive daytime sleepiness, improving nighttime sleep, and managing cataplexy symptoms if present. Since the medications are used on a long-term basis and have considerable adverse effects, treatment must balance maintaining an active life with avoiding adverse effects and developing tolerance to medications.

Table 21.4 summarizes various pharmacological treatment options based on symptoms of narcolepsy, and Table 21.5 gives an overview of medications used for narcolepsy.

Stimulants

Stimulants are indicated in the treatment of excessive daytime sleepiness. They produce substantial improvement in daytime alertness in a dose-dependent manner. Amphetamines and related drugs, which include methylphenidate, dextroamphetamine, and mixed amphetamine salts, are most commonly used. They increase dopaminergic and noradrenergic neurotransmission by blocking reuptake of these neurotransmitters via the dopamine reuptake transporter and by increasing presynaptic dopamine release (Riddle, Fleckenstein, & Hanson, 2005).

Stimulants are available in immediate-release and sustained-release forms. The usual duration of effect of immediate-release preparations is 3 to 6 hours. A combination of the two forms often provides the best balance between acute effects and sustained alertness. The optimal combination, timing, and dose to provide maximal efficacy vary on an individual basis. Patients may report "peaks" and "crashes" associated with the onset and offset of drug effects with short-acting preparations alone. Side effects may include increased heart rate and blood pressure and symptoms of anxiety, nervousness, and tremor. There have also been reports of methylphenidate causing an increased risk of sudden cardiac death, but Schelleman and colleagues found a lack of dose–response relationship, suggesting there may not be a causal association. Nocturnal sleep disruption can result from doses taken in the late afternoon and early evening. In some cases patients may experience psychotic symptoms such as hallucinations and paranoid delusions. Tolerance, dependence, and abuse can also occur. If tolerance develops, medication class can be switched or the patient can take periodic "drug holidays;" the latter may help to preserve the efficacy of stimulant medications.

Modafinil and armodafinil are wake-promoting agents comparable in efficacy to traditional stimulants in promoting alertness. Their exact mechanism of action is unknown but appears to involve local effects in the hypothalamus or effects on the dopamine transporter (U.S. Modafinil in Narcolepsy Multicenter Study Group, 2000). The effect of modafinil lasts relatively long due to its half-life of 12 to 15 hours.

TABLE 21.4 Hypersomnolence Disorders: Narcolepsy Treatment Based on Symptoms

Symptoms Addressed	*Key Clinical Points*	*Medications Used*	*Key References*
Excessive daytime sleepiness	Continuous daytime sleepiness with sleep attacks, usually the first symptom and present in 100% of the patients. Treatment includes conservative measures and medications.	Modafinil (standard) Sodium oxybate (standard) Amphetamine (guideline) Methamphetamine (guideline) Dextroamphetamine (guideline) Methylphenidate (guideline) Selegiline (option)	Littner et al., 2001 Wise, Arand, Auger, Brooks, & Watson, 2007
Cataplexy	Sudden usually bilateral, partial or complete loss of muscle tone provoked by emotional stimuli. Most accurate marker of the disease.	Sodium oxybate (option) Tricyclic antidepressants (option) Selective serotonin reuptake inhibitors (option)	Houghton, Scammell, & Thorpy, 2004 Dauvilliers, Arnulf, & Mignot, 2007 Lopez & Dauvilliers, 2013 Dauvilliers, Billiard, & Montplaisir, 2003
Sleep paralysis	Inability to move limbs or head or to speak or breathe normally either at sleep onset or awakening despite being mentally awake. May be associated with hypnagogic hallucinations.	Sodium oxybate (standard) Tricyclic antidepressants (guideline) Selective serotonin reuptake inhibitors (guideline) Venlafaxine (guideline) Selegiline (option)	Dauvilliers et al., 2003 La Herrán-Arita & García-García, 2013

The efficacy of modafinil has been evaluated extensively in excessive daytime sleepiness due to narcolepsy, idiopathic hypersomnia, and sleep apnea (La Herrán-Arita & García-García, 2013). Side effects include headache, nervousness, and small increases in blood pressure. Modafinil inhibits hepatic enzymes and can reduce the effectiveness of oral contraceptives (La Herrán-Arita & García-García, 2013; Littner et al., 2001).

Lisdexamfetamine is a pro-drug of d-amphetamine that has been used in children with attention-deficit/hyperactivity disorder. It provides a more gradual increase in brain drug concentrations, reducing pleasurable effects of the d-amphetamine. Increasing its dose enhances its efficacy but also delays its time of peak effect. This makes it less favorable for abuse and diversion purposes (Heal, Smith, Gosden, & Nutt, 2013). There have not been studies evaluating lisdexamfetamine specifically for narcolepsy, and it is not FDA approved for this indication but has been used as an "off-label" drug for treatment of narcolepsy.

Sodium oxybate can also enhance alertness in narcolepsy (Mamelak, Black, Montplaisir, & Ristanovic, 2004), but it is primarily used for the treatment of cataplexy. Atomoxetine and bupropion are other agents

TABLE 21.5 Medications for Narcolepsy

Medication/Medication Class	*Key Clinical Points*	*Main Side Effects*	*Evidence for Efficacy*	*Evidence Grade*	*Key References*
Nonamphetamine stimulants; for example modafinil (100–400 mg once daily or in divided doses) and armodafinil	For treatment of excessive daytime sleepiness. Mechanism of action is unknown but hypothesized to selectively activate wake-generating sites in the hypothalamus.	Headache, nausea, dizziness, insomnia	Results from many multicenter studies indicate significant impact of modafinil on sleepiness.	Type 1 and 2 studies	La Herrán-Arita & García-García, 2013 Golicki, Bala, Niewada, & Wierzbicka, 2010 Wisor & Eriksson, 2005, 2010
Amphetamine-like stimulants: Amphetamines 5–60 mg divided doses Methylphenidate 5–60 mg divided doses	Helpful in excessive daytime sleepiness. Increase dopamine transmission. Tolerance may develop requiring escalating doses. Effectiveness may be restored by "drug holiday."	Nervousness, headache, loss of appetite, palpitations, irritability, tremors	Currently available stimulants have not been tested parallel to placebo control or with each other in narcolepsy patients.	Type 2 and 3 studies	Mignot, 2012 Wisor et al., 2001 Heal et al., 2013 Mitler, Erman, & Hajdukovic,1993
Sodium oxybate 6–9 g of liquid solution divided nightly	Useful for cataplexy and excessive sleepiness in narcolepsy. Can cause rapid sedation and amnesia. Available only from a single central pharmacy.	Sedation, enuresis, respiratory suppression	Based on RCTs and case series	Type 1 & 3 studies	Anon., 2003 Mayer, 2012 Black & Houghton, 2006 Black, Pardi, Hornfeldt, & Inhaber, 2010
Selective serotonin reuptake inhibitors	Used for treatment of cataplexy. Less efficacious but better side effect profile compared to tricyclics.	CNS excitation, nausea, sexual difficulties	Based on case series and case reports	Type 4–6 studies	Lopez & Dauvilliers, 2013 Vignatelli, D'Alessandro, & Candelise, 2008 Frey & Darbonne, 1994 Langdon, Shindler, Parkes, & Bandak, 1986
Tricyclic antidepressants	Were the first medications to treat cataplexy; currently used as the last resort.	Dry mouth, urinary retention, constipation	-	Type 3 studies	Campos-Rodriguez et al., 2012 La Herrán-Arita & García-García, 2013 Schmidt, Clark, & Hyman, 1977 Roth, 2007
Norepinephrine and serotonin uptake inhibitors	Effective for cataplexy, sleep paralysis and hypnagogic hallucinations. Venlafaxine has been used in both adults and children. Atomoxetine is a highly specific noradrenergic reuptake inhibitor and tried in cases of resistant cataplexy after failure of fluoxetine, venlafaxine, and other serotonin reuptake inhibitors.	Nausea, dry mouth, elevated blood pressure, insomnia, withdrawal syndrome	Based on case series	Type 3 & 6 studies	Lopez & Dauvilliers, 2013 Møller & Østergaard, 2009 Ratkiewicz & Splaingard, 2013 Houghton et al., 2004

used in patients with hypersomnolence, but their efficacy has not been formally evaluated.

Anticataplectic Drugs

First-line treatment for cataplexy consists of antidepressants, mainly venlafaxine, desmethylvenlafaxine, duloxetine, or fluoxetine (Morgenthaler et al., 2007a).

Sodium oxybate (gamma hydroxybutyrate) is also a very effective treatment for cataplexy, with additional positive effects on daytime sleepiness (Anonymous, 2002, 2003). Sodium oxybate is administered in gram doses so it is given as a liquid at the beginning of the night and in the middle of the night. Two doses through the night are required because of its very short elimination half-life, ranging from 20 to 70 minutes. Although the half-life is very short, it exerts longer-lasting physiological effects through unknown mechanisms (Pardi & Black, 2006). It increases slow-wave sleep and REM sleep. Sodium oxybate is strictly controlled by the U.S. Drug Enforcement Agency because of its abuse potential and the possibility of diversion to other individuals. Side effects include profound sleepiness, sleepwalking, amnestic behaviors, and respiratory suppression in large doses.

BREATHING-RELATED SLEEP DISORDERS

Overview and Diagnosis

Breathing-related sleep disorders include three distinct disorders: obstructive sleep apnea hypopnea, central sleep apnea, and sleep-related hypoventilation. All of these are associated with impaired ventilation during sleep, resulting in sleep disruption and daytime fatigue or sleepiness. Effective treatment can have a positive impact on quality of life and morbidity of psychiatric patients. These disorders are also important to recognize in patients with psychiatric conditions because of symptom overlap, such as disrupted sleep, sleepiness, irritability, and depression (Harris, Glozier, Ratnavadivel, & Grunstein, 2009).

A careful history of symptoms followed by in-lab or at-home diagnostic polysomnography is warranted. A sleep study (polysomnogram) records breathing patterns in addition to other parameters. Two types of breathing events are typically identified: hypopneas, characterized by reduction in airflow by 30% with oxygen desaturation of at least 3%, and apneas, characterized by cessation of airflow for at least 10 seconds. The number of apneas and hypopneas per hour of sleep is known as the apnea-hypopnea index, which is a measure of severity of obstructive sleep apnea hypopnea and central sleep apnea. More than five events in one hour are considered abnormal in adults. Sleep-related hypoventilation may or may not be associated with an increased apnea-hypopnea index but is characterized by low oxygen saturation (hypoxemia) or carbon dioxide retention (hypercapnia).

Management

The goals of treatment for patients with obstructive sleep apnea syndrome are correcting the breathing disturbance, controlling symptoms, and reducing comorbidities associated with sleep apnea to improve quality of life. Table 21.6 summarizes treatments for obstructive sleep apnea.

Somatic Treatments

Positive Airway Pressure Therapy

Positive airway pressure therapy helps to passively open the upper airway during sleep and acts as a pneumatic splint. In addition, it may also increase upper airway size and stiffen the upper airway walls, likely due to "tracheal tug"—the downward pull on upper airway structures during lung expansion (Alex, Aronson, Onal, & Lopata, 1987).

RCTs have also shown positive airway pressure to improve sleepiness, quality of life, and blood pressure. Observational studies have shown reduction in cardiovascular mortality. Optimal adherence to therapy is a major limiting factor in reducing effectiveness (Campos-Rodriguez et al., 2012).

Various modes of positive pressure therapy delivery include continuous positive airway pressure, bilevel positive airway pressure, autotitrating positive pressure devices, and devices with a backup rate. Table 21.7 lists these devices and gives brief descriptions.

Oral Appliance Therapy

Oral appliances are devices that are inserted into the mouth for treatment of snoring and sleep apnea.

TABLE 21.6 Breathing-Related Sleep Disorders: Obstructive Sleep Apnea

Treatment Modality	*Key Elements*	*Evidence for Efficacy*	*Evidence Grade*	*AASM Grade*	*Key References*
Positive pressure therapy	First-line treatment. Main limitation is willingness to accept therapy and remain adherent. Many variants available, such as continuous, bilevel, or autoadjusting positive pressure therapy. Splints open airway while sleeping.	Based on various RCTs with strong evidence. Many studies have intention-to-treat designs. Studies to assess and validate a mechanical device such as continuous positive airway pressure are difficult to design.	Type 1–3 and 3 studies	Gold standard in moderate to severe cases and option in mild cases	McDaid et al., 2009 Epstein et al., 2009 Pagel, 2007 Campos-Rodriguez et al., 2012
Oral appliance	Device inserted in the mouth. Tongue retaining and mandibular repositioning. Minimum of 6–10 teeth in each arch is needed. Not recommended as first line in patients with severe obstructive sleep apnea, but may be considered if unable to tolerate positive airway pressure therapy or failed surgery.	Various RCTs have demonstrated efficacy of oral appliance in mild to severe cases. Better tolerated than positive pressure in some cases. Need to establish uniform definition of treatment success and patient characteristics associated with treatment success need to be determined.	Type 1, 4, 5 studies	Standard for primary snoring. Guideline for patients with mild to moderate obstructive sleep apnea who prefer or are not candidates for continuous positive airway pressure or cannot tolerate continuous positive airway pressure.	Ferguson et al., 2006 Hoffstein, 2007 Ngiam et al., 2013 Pliska & Almeida, 2012 Doff et al., 2013
Surgery	Tracheostomy was the first treatment option available. Evaluation of patients includes fiberoptic evaluation of upper airway. Various options available like maxillary mandibular advancement, uvulopalatopharyngoplasty, palatal implants or multilevel or stepwise approach.	Few systematic reviews and a very small number of RCTs. There is lack of high-level controlled studies and absence of standardized criteria to describe "surgical success."	Type 3–6 studies	Option as an adjunct to treatment of obstructive sleep apnea in obese patients. It can be used as first line in mild to moderate cases.	Aurora et al., 2010a Caples et al., 2010 Sommer, Maurer, Hörmann, & Stuck, 2012

(*continued*)

TABLE 21.6 (continued)

Treatment Modality	*Key Elements*	*Evidence for Efficacy*	*Evidence Grade*	*AASM Grade*	*Key References*
Medical management	Weight loss, modafinil for residual sleepiness, topical nasal corticosteroids for rhinitis, positional therapy	Few RCTs have evaluated adjunct treatments for obstructive sleep apnea. Weight loss has been well documented to have a positive impact on obstructive sleep apnea. Several studies documenting sleep position influencing severity of sleep apnea. Modafinil has been shown to improve residual sleepiness after treatment of sleep apnea in patients who do not have an identifiable cause of hypersomnolence based on few studies with variable level of evidence.	Type 1–6 studies	Option as an adjunct to primary treatment	Dixon et al., 2012 Sarkhosh et al., 2013 Neill, Angus, Sajkov, & McEvoy, 1997 Chapman et al., 2014 Darwish et al., 2010 Keating & Raffin, 2005 Schwartz, Hirshkowitz, Erman, & Schmidt-Nowara, 2003
Oxygen therapy	Oxygen therapy has not been proved to improve outcomes in obstructive sleep apnea. May be useful in treatment of severe hypoxemia untreated by positive pressure therapy.	Level 2 and level 3 studies, few of which were based on special-population patients. The evidence suggests that providing supplemental oxygen during sleep is not sufficiently effective in reducing apnea frequency and increasing daytime alertness to stand alone as therapy for most patients.	Type 2 and 5	Not recommended as primary treatment	Mehta, Vasu, Phillips, & Chung, 2013 Owens, 2013

TABLE 21.7 Positive Airway Pressure Delivery

Mode	*Mechanism of Pressure Delivery*
Continuous positive airway pressure (CPAP)	Continuous pressure during exhalation and inhalation
Bilevel positive airway pressure (BPAP)	Separate pressures during exhalation (lower) and inhalation (higher). Can be with or without a backup rate. Backup rate is helpful in patients who cannot generate effective breathing effort.
Autotitrating positive airway pressure	Minimum and maximum pressure fluctuates between set limits. Can be AutoCPAP or AutoBPAP.

Two main types are the tongue retaining device and mandibular repositioning appliances, also known as mandibular advancement devices. They are typically used in mild to moderate sleep apnea when patients cannot tolerate positive pressure therapy.

RCTs have demonstrated improvement in the apnea-hypopnea index, sleepiness, quality of life, and 24-hour blood pressure. Higher adherence to mandibular advancement devices is likely the cause of improved effectiveness compared to continuous positive airway pressure, despite lower efficacy. The most common minor and temporary side effects of therapy include temporomandibular joint pain, myofascial pain, tooth pain, salivation, dry mouth, gum irritation, and morning-after occlusion (Ferguson, Cartwright, Rogers, & Schmidt-Nowara, 2006; Pliska & Almeida, 2012).

Surgery

Various surgical procedures are available for management of upper airway obstruction. One of the most common is uvulopalatopharyngoplasty, but recent low-level evidence has shown that this procedure alone does not reliably normalize the apnea-hyponea index when treating moderate to severe sleep apnea. Low-level evidence has also shown another technique, maxillomandibular advancement, to be effective in the treatment of severe obstructive sleep apnea. Prior evidence has shown tracheostomy to be an effective single intervention to treat obstructive sleep apnea; however, concerns about patient safety, autonomy, and quality of life preclude its routine use, and it is considered only when deemed necessary by clinical urgency in cases of life-threatening obstructive sleep apnea and recurrent severe hypercapnic respiratory failure (Aurora et al., 2010a; Camacho et al., 2014; Caples et al., 2010).

Medical Management

Clinical trials have shown long-term improvements in sleep-disordered breathing and sleep quality from lifestyle interventions aimed at weight loss that include dietary modification and aerobic exercise, especially when combined with a primary treatment for obstructive sleep apnea (Dixon et al., 2012). In addition to dietary weight loss, bariatric surgery can be considered as an adjunctive treatment, especially in cases of morbid obesity. Positional therapy (avoiding the supine position) and reduction in alcohol use should be also considered as helpful measures in some patients.

The use of topical nasal steroids is recommended in patients with obstructive sleep apnea and concurrent rhinitis. Modafinil is recommended for treatment of residual excessive daytime sleepiness in patients with obstructive sleep apnea after effective positive airway pressure treatment has been provided and when no other identifiable causes of sleepiness have been identified (Morgenthaler et al., 2006).

CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS

Overview and Diagnosis

In humans, many physiological and behavioral processes occur roughly on a 24-hour or circadian cycle. The suprachiasmatic nucleus in the anterior hypothalamus is the master circadian pacemaker in mammals. External stimuli called *zeitgebers* entrain the nucleus to the light-dark cycle. Misalignment

between endogenous circadian rhythm and exogenous factors results in a variety of disorders, classified in *DSM-5* as circadian rhythm sleep-wake disorders. An essential feature for diagnosis is a persistent or recurrent pattern of sleep-wake disturbance resulting in a mismatch between endogenous rhythm and personal or societal demands. *DSM-5* distinguishes the following types of disorders.

Delayed sleep phase type is characterized by delayed sleep onset and awakening. Sleep duration and quality are normal when patients are allowed to sleep during their own "biological night." Advanced sleep phase type is characterized by a sleep cycle that is advanced compared to conventional societal norms. Irregular sleep-wake type occurs when the sleep-wake pattern is disorganized and variable throughout the 24-hour period; this type is commonly seen in neurodegenerative disorders and institutionalized elderly persons (Sack et al., 2007; Zee & Vitiello, 2009). Non-24-hour sleep-wake type is defined by a sleep pattern that is entrained to an endogenous circadian rhythm that is usually slightly more than 24 hours, accompanied by a daily drift usually to later times. It occurs commonly in blind individuals. Shift work type is associated with an unconventional shift work schedule, with insomnia during the time allotted for rest and/or excessive sleepiness while at work.

Diagnosis of these disorders is based on clinical presentation and thorough history. Sleep-wake logs are a useful tool to assess the sleep-wake pattern. Actigraphy can provide objective verification of activity and resting patterns. Polysomnography may be useful to rule out other sleep disorders, like obstructive sleep disorder or periodic limb movement disorder.

Management

Improved daytime function, nighttime sleep, and quality of life are the major treatment goals for circadian rhythm sleep wake disorders. The main approach in treatment is to realign the timing of the endogenous circadian rhythm with the required sleep-wake schedule. Bright light and melatonin can reset the circadian clock in a time-of-day–dependent manner when given at specific times. Bright light in the morning advances rhythms and in the evening delays them. Melatonin in the evening advances rhythm and in the morning (theoretically) delays rhythm. The "switch point" between advances and delays for both bright light and melatonin occurs at the time of core body temperature minimum, about 2 to 3 hours before habitual wake time. Consequently, bright light or melatonin close to the time of core body temperature minimum can have large and unpredictable effects on circadian rhythm timing.

Table 21.8 gives an overview of common treatments used in circadian rhythm sleep disorders. A treatment outline for specific disorders is given below.

Delayed Sleep Phase Syndrome

Treatment includes slowly advancing the circadian rhythm and avoiding bright light in the evening. Melatonin (0.5 to 5 mg) can be used to advance the sleep cycle when given 6 to 9 hours before the dim-light melatonin onset (~1 to 3 hours before sleep onset) (Mundey, Benloucif, Harsanyi, Dubocovich, & Zee, 2005). Bright light in the morning hours, near the time of usual awakening, also helps to advance circadian rhythms. Combination therapy with morning bright light and evening melatonin can improve subjective sleepiness, fatigue, and cognitive function (Wilhelmsen-Langeland et al., 2013). Good sleep hygiene is an essential component of treatment (see Table 21.3).

Advanced Sleep Phase Syndrome

Similar to delayed sleep phase syndrome, appropriately timed bright light and melatonin are used to treat advanced sleep phase. Bright light between 7 and 9 p.m. is used to delay the natural sleep-wake window and other circadian rhythms. Bright light should be avoided in the early morning to minimize phase-advancing effects. No published studies currently validate the effectiveness of morning melatonin in this disorder (Lack & Wright, 1993; Lack, Wright, Kemp, & Gibbon, 2005), and concerns about a direct sedating effect with morning administration weigh against this treatment.

Irregular Sleep-Wake Disorder and Non-24-Hour Sleep-Wake Disorder

Treatment of irregular sleep-wake cycle and non-24-hour sleep-wake cycle depends on whether a person has light perception. It mainly entails consolidating

TABLE 21.8 Circadian Rhythm Disorders

Treatment Modality	*Key Elements*	*Type of Disorder Addressed*	*Evidence for Efficacy*	*Evidence Grade*	*Key References*
Light therapy	Timed light exposure can shift circadian phase and increase objectively determined alertness. Exposure to bright light at the wrong circadian time can perpetuate or exacerbate changes in sleep-wake period.	Best evidence in delayed sleep phase syndrome but may be considered as an option in other circadian rhythm disorders	Cohort, case control studies, and case series	Type 2, 3, 4 studies	Morgenthaler et al., 2007b Wilhelmsen-Langeland et al., 2013
Melatonin	Important modulator of circadian rhythms. In addition to phase-resetting properties, evidence supports role in sleep modulation by increasing evening sleep propensity and reducing core body temperature.	Shift work, jet lag. Effective for entraining circadian rhythms in blind people with free-running sleep-wake cycles.	RCTs, cohort and case control studies	Type 2 & 3 studies	Morgenthaler et al., 2007b Wilhelmsen-Langeland et al., 2013 Weingarten & Collop, 2013 Cajochen, Kräuchi, & Wirz-Justice, 2003 Herxheimer & Petrie, 2001
Hypnotics	Can increase duration of daytime sleep but have not shown to improve alertness in early morning hours during shift work	Jet lag, shift work	RCTs, cohort and case control studies	Type 2 & 3 studies	Morgenthaler et al., 2007b Buxton, Copinschi, van Onderbergen, Karrison, & van Cauter, 2000 Walsh, Sugerman, Muehlbach, & Schweitzer, 1988
Chronotherapy	Successful delay of sleep times by 3 hours daily over a 5- to 6-day period until the desired sleep time is achieved. Followed by rigid adherence to a set sleep-wake schedule and good sleep hygiene practices. Light exposure at wrong time may limit effectiveness and practicality.	Delayed, advanced sleep phase disorders	Based on case reports and committee consensus	Type 3, 5, 6 studies	Morgenthaler et al., 2007b Singh, Sharma, & Malviya, 2012d
Stimulants	Modafinil and caffeine counter sleepiness and improve performance during night shift compared to placebo.	Shift Work Disorder (SWD), jet lag	Based on RCTs	Type 1, 2, 3 studies	Sack et al., 2007 Darwish, Bond, & Ezzet, 2012 Czeisler et al., 2005 Ker, Edwards, Felix, Blackhall, & Roberts, 2010

the sleep period. Melatonin, increased social cues, and bright light immediately after awakening are options for sighted individuals or blind people with intact retino-hypothalamic pathways. In blind individuals without light perception, lack of entrainment from environmental light cues is the main problem. Exogenous melatonin at a fixed time every day (dose range 0.3 to 10 mg approximately 1 hour before the desired bedtime) can help entrainment (Hack, Lockley, Arendt, & Skene, 2003). Tasimelteon, a melatonin receptor agonist, has recently been approved by the FDA, based on two trials, for the treatment of non-24-hour sleep-wake disorder in blind individuals.

Shift Work Disorder

The treatment of shift work disorder—specifically overnight shift work—includes interventions to (1) decrease sleep pressure at night (scheduled naps or hypnotics before daytime sleep), (2) increase alertness using caffeine or stimulants at the beginning of the work shift, and/or (3) minimize bright light exposure at the end of the work shift by wearing dark glasses while traveling home from work and using blackout curtains to make the bedroom as permissive for sleep as possible (Morgenthaler et al., 2007b). Bright light during the first half of the night shift may also help to delay circadian rhythms and improve shift work adaptation.

Modafinil and armodafinil are both FDA approved for use in shift workers with excessive sleepiness during work hours (Czeisler et al., 2005). On days off, night-shift workers may have regular daytime social or family responsibilities and often revert to nocturnal sleep hours. An experimental paradigm of "compromise phase position" has been promising wherein the individual goes to bed slightly earlier and does not completely invert his or her schedule on days off (Smith et al., 2009).

Jet Lag Disorder

The basic strategy for treatment includes symptom management and realigning circadian clock to the new time zone as soon as possible. American Academy of Sleep Medicine practice parameters consider timed melatonin administration as a "standard" and timed and dosed bright light as a treatment "option" for jet lag disorder. While traveling east, treatment should be started before travel. This involves gradually moving the sleep period before travel by 1 hour earlier each day and having the patient exposed to at least 1 hour of bright light in the morning. After arrival at the destination, light should be avoided in the morning, followed by exposure to high levels of light in the afternoon. Exogenous melatonin should be taken 5 hours before habitual bedtime. Hypnotics can be used at bedtime if needed at the destination. While traveling west, treatment should be started at the destination. Morning bright light should be avoided and light exposure in the evening should be maximized. Hypnotics can be taken at bedtime if needed. Good sleep hygiene and a 30-minute nap during the day are a helpful adjuncts in cases of both east and west travel.

Combination therapy with somatic and behavioral interventions, including a regular sleep schedule and good sleep hygiene, is usually beneficial for all circadian rhythm sleep-wake disorders.

PARASOMNIAS

According to *DSM-5*, the parasomnias include sleep disorders with undesirable physical events or experiences that occur at entry into sleep, during sleep, or during arousals from sleep. They include NREM sleep arousal disorders, nightmare disorders, and REM sleep behavior disorder. Many of them are benign, especially during childhood, but they can cause physical harm and poor health due to sleep disruption.

NREM Sleep Arousal Disorders

Overview and Diagnosis

NREM sleep arousal disorders include parasomnias that occur from arousals during NREM sleep, most often sleep stage N3 or slow-wave sleep. They include confusional arousals, sleep terrors, and sleepwalking. Other specific behaviors may include sleep-related eating disorder and sleep-related sexual activity. *DSM-5* defines three specific ones—NREM parasomnias, sleepwalking, and sleep terrors. Recurrent episodes of partial arousals from sleep occur usually during the first third of the night, when NREM sleep is deepest. There is typically minimal or no recall of the event, with minimal or no dream imagery.

TABLE 21.9 Nightmare Disorder

Treatment Modality	*Key Elements*	*Evidence for Efficacy*	*Evidence Grade*	*Key References*
Nonpharmacological	Trauma-focused cognitive-behavioral therapy, including imagery rehearsal technique; lucid dreaming therapy; sleep dynamic therapy; relaxation; and rescripting therapy and self-exposure therapy	Based on case series and case studies. Some case control studies.	Type 3 and 6 studies	Bisson, Roberts, Andrew, Cooper, & Lewis, 2013 Bisson & Andrew, 2007 Germain, Buysse, & Nofzinger, 2008 Augedal et al., 2013
Prazosin	For nightmares associated with post-traumatic stress disorder. Postural hypotension.	Based on 3 RCT/placebo-controlled studies and some case series. Found to be moderate to strongly beneficial.	Type 2 and 3 studies	Augedal et al., 2013 Hudson, Whiteside, Lorenz, & Wargo, 2012 Aurora et al., 2010b Taylor, Freeman, & Cates, 2008
Clonidine	Nightmares associated with posttraumatic stress disorder	No RCTs. Paucity of hard data.	Type 3 studies	Alao, Selvarajah, & Razi, 2012 Aurora et al., 2010b

Sleepwalking is characterized by repeated episodes of rising from bed and walking about during sleep. During the episodes, the individual has reduced alertness and responsiveness, blank stare, and absent communication with others. There is relative unresponsiveness to efforts by others to awaken the individual, and if awakened he or she has limited recall of the episode.

Sleep terrors include repeated sudden awakenings from sleep, usually with a scream or cry. Excessive autonomic arousal and behavioral manifestations of intense fear occur. The individual is difficult to awaken or difficult to comfort during the episode. Sleep terrors are also called "night terrors" or "pavor nocturnus."

Confusional arousals are not specifically included in a part of *DSM*-5 but are considered to be related to other NREM parasomnias. Confusional arousals are brief, incomplete arousals that start in N3 sleep. During episodes, the individual usually does not leave the bed. Primary sleep disorders such as sleep apnea or periodic limb movement disorders can aggravate these conditions.

Sleep-related eating disorder is classified as a subtype of sleepwalking in *DSM*-5. It involves partial arousals from sleep in which the patient involuntarily eats and drinks. It can occur in isolation or comorbidly with restless legs syndrome, periodic limb movements, and sleep-related breathing disorders (Howell, Schenck, & Crow, 2009).

Sleep-related sexual behavior ("sexsomnia") is also classified as a subtype of sleepwalking in *DSM*-5. It consists of inappropriate sexual behaviors during sleep without conscious awareness and may have medicolegal implications. This may result in feelings of shame or guilt leading to depression (Schenck, Arnulf, & Mahowald, 2007).

Management

Treatment of NREM parasomnias is directed at reducing symptoms of self-harm or harm to others based on the frequency of events (Mahowald & Cramer Bornemann, 2005).

Somatic Treatment

Clonazepam (0.5 to 1 mg) has been successful in the long-term management of parasomnias. If the disorder is limited to the first half of the sleep period, short-acting benzodiazepine receptor agonists such as triazolam or zolpidem have been used. Dopaminergic agents, opiates, and topiramate have been used and found to be effective in sleep-related eating disorder. If nonpharmacological treatment is not enough to manage symptoms, use of pharmacotherapy may be helpful in the treatment of sleepwalking (Schenck & Mahowald, 2000, 2002).

Psychosocial and Behavioral Treatments

Reassurance about the benign nature of childhood NREM parasomnias, especially in episodic cases, is usually sufficient. For more severe episodes, nonpharmacological treatments have been found to be helpful in children. These include maintaining a regular sleep-wake schedule and reducing sleep pressure by avoiding sleep deprivation. For sleepwalking, ensuring a safe sleeping environment is crucial to management, which would include safety locks on doors. NREM parasomnia episodes may be triggered by sleep disruption due to obstructive sleep apnea or periodic limb movement disorder. These cases may benefit from treatment of the primary sleep disorder (Schenck & Mahowald, 2010).

Nightmare Disorder and REM Sleep Behavior Disorder

Overview and Diagnosis

REM sleep is characterized by increased physiological activation, atonia of muscles, and dreams or active mentation. The most common parasomnias occurring during REM sleep are REM sleep behavior disorder and nightmare disorder. REM sleep behavior disorder is characterized by loss of normal muscle tone along with dream enactment (often violent). According to *DSM-5*, the presence of atonia during REM sleep on a polysomnogram or a history suggestive of REM sleep behavior disorder, along with a diagnosis of alpha synucleinopathy (e.g., Parkinson's disease), can be used to diagnose REM sleep behavior disorder.

Nightmare disorder is characterized by recurrent disturbing dreams during REM sleep, often resulting in awakening, distress, and impairment of daytime function.

Management

Treatment of REM parasomnias is directed at reducing symptoms of self-harm or harm to others based on the frequency and bothersome nature of events. Table 21.10 lists treatment options for REM behavior disorder.

TABLE 21.10 REM Parasomnia—REM Sleep Behavior Disorder

Treatment Modality	*Key Elements*	*Evidence for Efficacy*	*Evidence Grade*	*Key References*
Clonazepam	Long-acting benzodiazepine. May preferentially control phasic locomotor activity at the brain stem level without restoring atonia via a serotonergic effect. May also modify dream content in REM sleep behavior disorder.	Based on case series and case reports	Type 3 and 5 studies	Aurora et al., 2010c Fantini & Ferini-Strambi, 2012
Melatonin	Studies show success in patients with synucleonopathies, memory problems and sleep-disordered breathing. Decreased episodes of REM sleep without atonia and movement time in REM, as opposed to studies with clonazepam.	Evidence less strong than for clonazepam. Based on clinical consensus. Case series with very few subjects.	Type 2, 3, 6 studies	Aurora et al., 2010c Kunz & Mahlberg, 2010 Anderson & Shneerson, 2009 Boeve, Silber, & Ferman, 2003
Nonpharmacological	Injury-prevention techniques. Modifying sleep environment has best evidence for treatment of REM sleep behavior disorder.	Consensus-based recommendation by American Academy of Sleep Medicine	Type 6 studies	Aurora et al., 2010c Schenck, Lee, Bornemann, & Mahowald, 2009
Dopamine agonist—pramipexole	PET and SPECT scans have suggested dysfunction of dopaminergic nigrostriatal system, due to which dopamine agonists have been considered.	Efficacy studies have shown contradictory results.	Type 3 and 6 studies	Aurora et al., 2010c Sasai, Inoue, & Matsuura, 2012 Schmidt, Koshal, & Schmidt, 2006

REM Sleep Behavior Disorder

Benzodiazepine receptor agonists are the first-line treatment of REM sleep behavior disorder. Clonazepam (0.5 to 1 mg) is the most commonly used medication. Not only does it reduce the frequency of events, but it may also modify dream content in REM sleep behavior disorder. Melatonin and pramipexole have also been used with some success (Aurora et al., 2010c). Ensuring the safety of the sleep environment for the patient and his or her bed partner is an essential adjunct to treatment. Medication-induced cases usually resolve after discontinuing the offending agent (Mahowald & Schenck, 2005).

Nightmare Disorder

Prazosin has been shown to be effective in RCTs for treatment of nightmare disorder associated with posttraumatic stress disorder (Cukor, Spitalnick, Difede, Rizzo, & Rothbaum, 2009). Medications, including benzodiazepines and sedating antidepressants such as trazodone, are used to treat nightmares, but little empirical evidence supports their efficacy. Dream rehearsal therapy is useful for recurrent nightmares. This treatment involves scripting and rehearsing a new dream scenario to replace the common, distressing dreams (Augedal, Hansen, Kronhaug, Harvey, & Pallesen, 2013). Table 21.9 summarizes some treatment modalities for nightmare disorder.

RESTLESS LEGS SYNDROME

Overview and Diagnosis

Restless legs syndrome is a sensorimotor neurological disorder causing uncomfortable sensations in the leg that are described by patients as aching, burning, tingling, creeping, crawling, or "pins and needles" (Kerr, McKinon, & Bentley, 2012). *DSM-5* describes restless legs syndrome as an urge to move the legs that worsens during rest and in the evenings and is relieved by moving around. There may be associated repetitive leg jerks at night during sleep, which are called periodic limb movements (Rye & Trotti, 2012). These limb movements are characterized by rhythmic, repetitive stereotypic dorsiflexion/extension of the big toe, dorsiflexion at the ankle, and sometimes flexion at the knee and hip joints. For the leg movements to be counted as periodic limb movements, they must be 0.5 to 10 seconds in duration and have an amplitude greater than 8 μV above the resting baseline anterior tibial electromyogram level on a polysomnogram. The periodic limb movement index is defined as the number of these movements per hour of sleep. An index above 15 in adults and above 5 in children is considered diagnostic for periodic limb movement disorder in the ICSD-2 (International Classification of Sleep Disorders-2) diagnostic and coding manual.

Improvements in restless legs syndrome and periodic limb movement disorder seen with L-dopa and dopamine agonists support the hypothesis that dopamine may be involved in the pathophysiology of these disorders (Cervenka et al., 2006). Restless legs syndrome may be idiopathic (primary) or secondary. Those with an affected first-degree relative commonly have primary restless legs syndrome. Secondary causes include renal failure, pregnancy, iron deficiency, and medications. Iron is an important co-factor in the dopamine synthesis pathway. It is also necessary for intracellular mitochondrial function in dopamine-producing neurons (Yeh, Walters, & Tsuang, 2012).

Management

The goals of treatment of restless legs are to improve symptoms that result in disturbances in sleep onset or sleep maintenance, causing sleep disruption and daytime sleepiness. Treatment options are outlined in Table 21.11.

Somatic Treatment

Evaluation and treatment of reversible causes should be first attempted. A serum ferritin level less than 50 mcg/dL should be treated with iron replacement therapy. Vitamin B_{12}, folate, vitamin D, and magnesium deficiency should also be treated (Cuellar, Hanlon, & Ratcliffe, 2011).

Dopamine agonists, including pramipexole and ropinirole, are considered as first-line therapy and have been tested in controlled trials for treatment of restless legs syndrome. The most common side effects are sleepiness, nausea, and hypotension. They may be associated infrequently with compulsive gambling, spending, or sexual behavior. Rotigotine is a non-ergot dopamine receptor agonist available in a transdermal patch form (Bogan, 2014).

TABLE 21.11 Restless Legs Syndrome

Treatment Modality	*Key Elements*	*Side Effects*	*Evidence for Efficacy*	*Evidence Grade*	*Key References*
Dopamine agonist—pramipexole, ropinirole	First line	Nausea, orthostatic hypotension, daytime fatigue and somnolence, compulsive or impulsive behavior, tolerance and augmentation	Based on double-blind placebo-controlled studies with long-term follow-up studies showing sustained efficacy	Type 1 & 2 studies	Aurora et al., 2012 Manconi et al., 2011 Scholz, Trenkwalder, Kohnen, Riemann, Kriston, & Hornyak, 2011a Varga et al., 2009 Zintzaras et al., 2010
Dopamine precursors (e.g., L-dopa/carbidopa)	Quick onset and short duration of action due to higher rebound	Morning rebound or augmentation in early evening, daytime somnolence	Open-label placebo-controlled studies	Type 3, 5, 6 studies	Bassetti et al., 2011 Scholz, Trenkwalder, Kohnen, Riemann, Kriston, & Hornyak, 2011b Trenkwalder et al., 2008
Opiates	Useful in severe cases, when patients are unresponsive to other agents. Useful during withdrawal from dopamine agonist after severe augmentation.	Constipation, dependence, respiratory depression at high doses. Use with caution in patients who snore and have sleep apnea.	Several open-label and controlled clinical trial	Type 2, 3, 5 studies	Walters, 2013
Benzodiazepine rector agonists	Used to improve quality of sleep and reduce periodic leg movements associated with arousals. Improves sleep continuity.	Sedation, ataxia, anterograde amnesia, sleepwalking, sleep violence or sleep-related eating disorders, respiratory depression. Rebound insomnia, tolerance, and abuse may occur.	Based on placebo-controlled crossover studies and case series	Type 2 and 6	Shinno et al., 2010 Facheris, Hicks, Pramstaller, & Pichler, 2010 Saletu et al., 2001
Anticonvulsants—Neurontin	More potent and fewer side effects than dopaminergic agonists. Useful in neuropathic restless leg syndrome.	Daytime fatigue and somnolence	Open-label and one placebo-controlled study	Type 1, 2, 6 studies	Burke & Faulkner, 2012 Yaltho & Ondo, 2010 Hayes, Lemon, & Farver, 2012 Lee et al., 2011

(*continued*)

TABLE 21.11 (continued)

Treatment Modality	*Key Elements*	*Side Effects*	*Evidence for Efficacy*	*Evidence Grade*	*Key References*
Iron supplementation	Iron deficiency and conditions involving iron deficiency such as end-stage renal disease, pregnancy, gastric surgery have been associated with secondary restless legs syndrome. Iron deficiency in substantia nigra may be associated with abnormal regulation of transferrin receptor. Most clinicians recommend achieving a ferritin level of >45 to 50 mcg/mL.	Constipation, nausea, gastrointestinal upset, dark stools	Based on RCTs	Type 1–3 studies	Hornyak et al., 2014 Mohri et al., 2012 Trotti, Bhadriraju, & Becker, 2012 .
Nonpharmacological	Good sleep hygiene; avoid alcohol use; stretching exercises and leg massages	NA	NA	Type 3 and 6 studies	Hornyak et al., 2014 Aurora et al., 2012 Romenets & Postuma, 2013

Levodopa/carbidopa is a dopaminergic medication that can also decrease restless legs syndrome symptoms and periodic limb movements. Augmentation and rebound effects are common with these medications. Augmentation is the tendency for symptoms to develop earlier in the day or to become more severe than prior to treatment and is usually treated by switching to a dopamine agonist (Cuellar et al., 2011; Romenets & Postuma, 2013; Silber, Becker, Earley, Garcia-Borreguero, & Ondo, 2013; Wilt et al., 2013).

Other medications include benzodiazepines, which can decrease arousals but do not decrease the number of movements, and opioids, which are also used for some treatment-resistant cases. Anticonvulsants such as gabapentin and carbamazepine can also be considered. Gabapentin may be useful in cases of restless legs associated with painful sensations (Silber et al., 2013).

Psychosocial and Behavioral Treatments

Nonpharmacological treatments that have been helpful include stretching exercises, massage, and hot baths. Avoiding tobacco, alcohol, caffeine, and antihistamines can also help decrease symptoms. If restless legs syndrome occurs during treatment with a selective serotonin reuptake inhibitor, switching to a different class of medication may be helpful (Hening, Buchfuhrer, & Lee, 2007).

SUMMARY

Treatment of sleep disorders can be initiated in most cases by non-sleep specialists. A significant number of patients seen in psychiatry clinics experience sleep disturbances. Most patients with insomnia can be treated by psychiatrists, especially given the coexistence of psychiatric disorders and insomnia. The close relationship that psychiatrists have with their patients provides an understanding of the biopsychosocial context in which their patients live, something that is undoubtedly important in successful treatment of sleep disorders. Referral to sleep specialists should be considered when there is evidence of coexisting multiple sleep disorders or when insomnia is complicated by evidence of other sleep disorders, such as sleep apnea or narcolepsy. Patients who do not respond to brief behavioral interventions or who fail to respond to conventional management options may also be good candidates for referral.

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22

Pharmacotherapy and Psychotherapy for Sexual Dysfunctions

R. Taylor Segraves

Well-controlled, double-blind, multisite (type 1) investigations have demonstrated that phosphodiesterase type 5 (PDE5) inhibitors are efficacious for the treatment of erectile problems of mixed etiologies and that serotonergic antidepressants delay ejaculation in men with premature ejaculation. Similarly, studies have demonstrated the efficacy of transdermal testosterone therapy in restoring sexual function in women after oophorectomy. Both type 1 and type 2 studies have produced suggestive evidence of the efficacy of cognitive-behavioral therapy (CBT) in the treatment of sexual dysfunction in both sexes, although the number and the methodological rigor of such studies are limited and the effect sizes tend to be smaller than studies of pharmacological therapies. There is minimal evidence concerning when pharmacological, as opposed to psychological, therapies should be employed, or when combined psychotherapy and pharmacotherapy is indicated. Major changes have been made in the definitions of sexual dysfunctions and their criteria sets in *DSM*-5. Existing data concerning the efficacy of both psychological therapies and pharmacotherapy may not extend fully to the sexual dysfunctions as defined in *DSM*-5.

INTRODUCTION

Most contemporary clinicians conceptualize sexual function as being influenced by biological, psychological, and cultural factors. Many cases of sexual dysfunction are precipitated and maintained by a combination of psychological and biological factors. The response to pharmacotherapy may itself be influenced by psychological factors. Even when the sexual dysfunction has predominantly biogenic origins, the existence of the problem may then produce psychological and interpersonal consequences that then complicate treatment.

Unfortunately, research concerning biological therapies has occurred relatively independently from research concerning psychotherapy of the sexual disorders. Research on biological therapies has tended to focus primarily on the target symptom, whereas psychotherapy tends to have a broader focus. Much of the current research concerns idiopathic sexual dysfunction in heterogeneous patient populations in which it is difficult to ascertain the relative contribution of biological and psychological factors. Thus, it is often unclear how much one can generalize from the published data to a given patient. Knowing the relative contribution of etiological factors is important since one would expect the benefits of psychotherapy to be less in cases that are primarily biological in etiology. One also would expect that the type of psychotherapy indicated in cases of predominantly biological etiology would be different in content from therapy designed to treat psychogenic sexual dysfunction. Since much of the current research is on heterogeneous or poorly defined populations, it is difficult to ascertain which type of intervention should be primary or when different interventions should be combined.

The current diagnostic systems may be partially responsible. The *DSM-IV-TR* was criticized for being

imprecise and not clearly differentiating transient variations in sexual functions in response to the vicissitudes of relationships from more enduring sexual difficulties. The *DSM-5* represents a marked departure from *DSM-IV-TR* and contains clear duration and severity criteria for sexual dysfunction. In addition, the *DSM-5* clearly specifies that a diagnosis of sexual dysfunction should not be made if the problem is secondary to relationship discord or life stress. It is hoped that these more precise criteria will facilitate research that will more clearly delineate the indications and advantages of different types of therapeutic interventions.

HISTORICAL OVERVIEW OF THERAPY FOR SEXUAL PROBLEMS

Historically, the treatment of sexual dysfunctions can be divided into five eras: the psychoanalytic, the early behavioral, the Masters and Johnson, the neo–Masters and Johnson, and the current psychobiological. Prior to 1970, psychoanalytic concepts guided clinicians in their understanding and treatment of sexual problems. Sexual symptomatology was linked to discrete, unresolved, unconscious conflicts that occurred during specific developmental periods. Sexual symptoms were traced to designated constellations of conflict occurring in early childhood (Meyer, 1976). In a classical analysis, patients were seen three to five times weekly over the course of several years. Freud's revolutionary method employed free association, dream analysis, interpretation of unconscious motives, and the recapitulation of significant emotional attachments through the transference. Because of the focus on individual intrapsychic dynamics, couples treatment was rarely undertaken. The analytic literature was replete with elegant, richly detailed descriptions of individual case histories and analysis. By contemporary standards, these often fascinating reports qualify only as untested case formulations.

In the late 1950s, behavioral therapists described promising results from treating sexual disorders by using of symptom-oriented direct treatment approaches (Brady, 1966; Cooper, 1969; Haslam, 1965; Lazarus, 1963; Wolpe, 1958). These interventions were loosely modeled on classical conditioning paradigms and assumed that the dysfunction was a learned (conditioned) anxiety response. The guiding principle of behavior therapy (LoPiccolo & LoPiccolo, 1978; Marks, 1981; Obler, 1973) was to extinguish the anxiety or performance demands that interfered with normal sexual function. The most common behavioral technique, systematic desensitization, paired relaxation with a series of carefully designed, hierarchical, anxiety-provoking sexual situations, in vivo or by imagery. Like psychoanalysis, behavior therapy concentrated on individual psychotherapy and tended to ignore the dynamics of relationships. These studies, while more rigorously documented than the analytic reports, had minimal influence on clinical practice.

In 1970, Masters and Johnson published the results of a study of 790 cases employing a blend of intense daily individual and couples psychotherapy for two weeks. The ingredients of their treatment model consisted of physical examination, history taking, education, prescription of behavioral tasks, and counseling for interpersonal issues that interfered with natural sexual function. Their treatment was based on two fundamental postulates: (a) the primacy of psychogenic factors, particularly learning deficits and performance anxiety in the etiology and maintenance of sexual dysfunctions, and (b) the amenability of most sexual disorders to a brief problem-focused treatment approach (Rosen & Leiblum, 1995). Masters and Johnson's most important contribution was the emphasis given to the deleterious effects of performance anxiety and their prescription of sensate focus exercises to alleviate this troubling state. Performance anxiety, the fear of future sexual failure based on a previous failure, is a universal experience that appears in all sexual dysfunctions. Masters and Johnson provided clear descriptions of their treatment method and reported initial and 5-year-posttreatment "failure rates" for lifelong and acquired arousal, orgasm, and pain disorders. Their work revolutionized the treatment of sexual problems and generated great enthusiasm among clinicians for their novel short-term, directive treatment methods.

By present-day standards, Masters and Johnson's outcome data can be criticized on multiple grounds, for not (a) using standardized, valid, and reliable assessment measures; (b) specifying the basis for classifying cases as successes or failures; (c) employing control, waitlist, or placebo groups; and (d) blinding the investigators to the experimental conditions. In addition, it was questionable whether their results applied to typical patient populations because they studied affluent, well-educated, and highly motivated

patients. These vital concerns linger because later researchers have been unable to replicate the magnitude of the positive outcomes achieved by Masters and Johnson (Heiman & LoPiccolo, 1983; Rosen & Beck, 1988; Wright, Perreault, & Mathieu, 1977; Zilbergeld & Evans, 1980). Nonetheless, their reports revolutionized the treatment of sexual problems and generated great enthusiasm among clinicians for their treatment method.

The neo–Masters and Johnson era was heralded by the publication of Helen Singer Kaplan's widely acclaimed book *The New Sex Therapy* (1974). As a discipline, sex therapy had come of age. Kaplan integrated modifications of Masters and Johnson's treatment methods with behavioral and analytic interventions. She treated couples by addressing both partners' intrapsychic and interpersonal contributions to the initiation and maintenance of the dysfunction. She distinguished between recent and remote etiological causation, recommending direct treatment approaches for the former while reserving traditional psychodynamic methods for the latter. The more commonly seen recent etiological causes were relationship deterioration, performance anxiety, widowhood, health concerns, and aging. Examples of remote influences included pre-Oedipal separation-individuation conflicts, unresolved Oedipal struggles, paraphiliac scripts, gender identity conflicts, and adolescent masturbatory guilt. Kaplan's prolific writings did not include outcome statistics on the follow-up of her suggested treatment interventions.

Treatments for sexual dysfunction proliferated and evolved into blends of psychodynamic, behavioral, and cognitive therapies using individual, couples, and group formats (Althof, 1989; Gagnon, Rosen, & Leiblum, 1982; Leiblum, Rosen, & Pierce, 1976; Levine, 1992; McCarthy & McCarthy, 1984; Rosen & Leiblum, 1989; Scharf, 1985; Zilbergeld, 1992). As the field matured, clinical investigators began to develop more sophisticated methodologies that included control groups, placebo treatments, randomization of experimental conditions, and standardized, valid, and reliable questionnaires. However, the majority of these research reports lacked long-term follow-up.

The middle 1980s ushered in the current psychobiological era. Sophisticated studies with adequate long-term follow-up describing the efficacy and psychological impact of oral agents, intracavernosal injection, vacuum tumescence therapy, and treatment of rapid ejaculation by serotonin reuptake inhibitors began to appear in the literature (Althof, 1995a, 1995b; Althof et al., 1995; Assalian, 1988; Barada & McKimmy, 1994; Goldstein et al., 1998; Segraves, Saran, Segraves, & Maguire, 1993). These studies turned the tide toward the blending of medical and psychological treatments for male sexual dysfunction.

In March 1998, sildenafil citrate received approval by the U.S. Food and Drug Administration (FDA) for the treatment of erectile dysfunction (ED; Goldstein et al., 1998). Since its release, countless prescriptions have been written, making it one of the most prescribed medications in the United States. Subsequently, vardenafil, tadalafil, and avanafil were also approved as PDE5 inhibitors for the treatment of ED (Goldstein et al., 2012; Wylie & MacInnes, 2005). The PDE5 inhibitors transformed the treatment and research landscape. Because the oral erectogenic agents were safe and easily tolerated, the established principle of etiology guiding treatment became less meaningful. Prior to the introduction of these treatments, men diagnosed with psychogenic ED were treated by mental health professionals and those with organic dysfunction were seen primarily by urologists. After the introduction of the oral erectogenic drugs, much of the care of such patients shifted to primary care physicians. These therapies altered the traditional role of the mental health professional, which had been to (a) assess the etiology of ED, (b) offer psychotherapy to men or couples with primarily psychological dysfunction, and/or (c) treat the conspicuous psychological sequelae of organic conditions (Althof & Seftel, 1995; Levine, 1992). Once these new pharmacological interventions became available, the clinician's role was shifted to include identification and attenuation of the resistances to medical treatments for ED.

Dapoxetine, a serotonin reuptake inhibitor, has been approved in many countries for the treatment of premature ejaculation (Hoy & Scott, 2012; McMahon, 2012). As a result, treatment of premature ejaculation has become predominantly pharmacological in the past decade.

Since 1999, the medicalization of sexual dysfunction has also begun to influence treatments for female sexual dysfunction. There have been studies of sildenafil for female sexual arousal disorder, testosterone patches to enhance sexual desire, and the introduction of clitoral erection devices, gels, and

homeopathic remedies as well (Berman, Shuker, & Goldstein, 1999). Although there was minimal evidence supporting a role for sildenafil in treating sexual arousal disorders (Laan, Everaerd, & Both, 2005), numerous studies found that exogenous testosterone increased libido in women with a decrease in libido after bilateral oophorectomy (Basson et al., 2004; Buster et al., 2005; Shifren et al., 2000; Utian, Braunstein, Buster, Lucas, & Simon, 2004). Use of testosterone therapy has been approved for the treatment of sexual problems in surgically menopausal women in some European countries, and considerable off-label use of testosterone occurs worldwide (Fooladi & Davis, 2012).

NOSOLOGY

Knowledge concerning the treatment of sexual dysfunctions and interest in this area of psychobiology has grown significantly in the past 20 to 30 years. The recent emergence of this field can be appreciated by realizing that the first two *DSM* editions (American Psychiatric Association [APA], 1952, 1968) did not contain diagnostic terms for the sexual dysfunctions. *DSM-III* (APA, 1980) provided a radical departure by including a section on sexual dysfunctions. These diagnoses and their criteria sets were based on the concept of a normal sexual response cycle for men and women (Schmidt, 1995) and were strongly influenced by the works of Masters and Johnson (1966) and Helen Singer Kaplan (1974). *DSM-IV* was introduced in 1994 and added two new entities: sexual dysfunction due to a general medical condition and substance-induced sexual dysfunction. There were no significant changes to the sexual dysfunction criteria in *DSM-IV-TR* (2000). Changes in nomenclature for the psychosexual dysfunctions in the different *DSM* versions are listed in Box 22.1.

Sexual dysfunctions listed in *DSM-IV* included male hypoactive sexual desire disorder (HSDD), ED, premature (early) ejaculation, delayed ejaculation, genito-pelvic pain/penetration disorder (GPPD; new to this edition), female sexual interest/arousal disorder (new to this edition), female orgasmic disorder, and substance/medication-induced sexual dysfunction. Five *DSM-IV-TR* diagnoses were deleted in *DSM-5*: sexual aversion disorder, female arousal disorder, dyspareunia, vaginismus, and sexual dysfunction secondary to a general medical condition. There were also some name changes: Male orgasmic disorder became delayed ejaculation and premature ejaculation became premature (early) ejaculation. In *DSM-IV-TR*, HSDD and dyspareunia applied to both sexes. *DSM-5* retained male HSDD, but features of female HSDD are now classified in a new entity, female sexual interest/arousal disorder. In *DSM-5*, features of dyspareunia and vaginismus are classified as GPPD. Dyspareunia in males no longer exists as a separate coding. Specific frequency and/or duration criteria are listed for all diagnoses except substance/medication-induced sexual dysfunction. A specific

BOX 22.1 Modifications in Sexual Disorders Nomenclature in the *Diagnostic and Statistical Manuals* of the American Psychiatric Association

1. *DSM-I* was published in 1952 and did not contain diagnostic terms for the psychosexual dysfunctions.
2. *DSM-II* was published in 1968. The only diagnostic entity pertaining to psychosexual disorders was psychophysiological genitourinary disorders, which referred to disorders of micturition, menstruation, and sexual function.
3. *DSM-III* was published in 1980. It included diagnoses for the psychosexual disorders. The term *homosexuality* was deleted and the term *ego dystonic homosexuality* was added as a diagnostic entity. The term *inhibited sexual excitement* referred to both male erectile disorder and female arousal disorder.
4. *DSM-III-R* was published in 1987. The term *sexual aversion disorder* was added. The term *ego dystonic homosexuality* was deleted. The use of the term *inhibited* in diagnostic entities was deleted. The term *inhibited sexual excitement* was changed to *male erectile disorder* and *female arousal disorder*.
5. *DSM-IV* was published in 1994. Subjective criteria were dropped from definitions of male erectile disorder and female arousal disorder. The terms *sexual disorder secondary to a general medical condition* and *substance-induced sexual disorder* were added.
6. *DSM-IV-TR* was published in 2000. Sexual dysfunction diagnoses were unchanged from *DSM-IV*.
7. *DSM-5* was published in 2013. Sexual disorder secondary to a general medical disorder, sexual aversion disorder, dyspareunia, vaginismus, female arousal disorder, and hypoactive sexual arousal disorder in females were deleted. Genito-pelvic pain/penetration disorder and female sexual interest/arousal disorder were added as new diagnostic categories. Specific duration and frequency criteria were added for most diagnostic categories.

time duration after vaginal penetration is specified for the diagnosis of premature (early) ejaculation. The diagnostic entities in *DSM-IV* are listed in Box 22.2, the additional specifications in *DSM-5* are listed in Box 22.3, and the major changes from *DSM-IV-TR* are listed in Box 22.4.

There have been a number of major changes in *DSM-5*. These changes are important to note as they may influence how much one can generalize from data using *DSM-IV-TR* diagnostic criteria to the new criteria. It is hoped that the new criteria will facilitate future clinical research by defining more homogenous groups. *DSM-IV-TR* criteria were criticized for being imprecise (Waldinger & Schweitzer, 2008), for not differentiating transient variations in sexual function from persistent sexual disorders meriting medical intervention (Segraves et al., 2007), and for assuming that female patterns of sexual response follow the same patterns as that of males (Basson, 2010). *DSM-5* represents a paradigm shift in that it recognizes that male sexuality and female sexuality are different and should be classified separately. For instance, in *DSM-5* male desire and arousal (erection) difficulties are classified as separate disorders, and the *DSM-5* diagnosis of female sexual interest/arousal disorder combines elements of sexual interest/desire with elements of subjective sexual arousal. Because of the high comorbidity of HSDD and female sexual arousal disorder as defined in *DSM-IV-TR* (Brotto, 2010; Graham, 2010), one assumes that research using *DSM-IV-TR* criteria will be largely applicable to the *DSM-5* category of sexual interest/arousal disorder. Studies at multiple centers have reported difficulties differentiating cases of vaginismus from dyspareunia (Binik, 2010a, 2010b). There is a new category, GPPD, in *DSM-5*. It is unclear whether data using the *DSM-IV-TR* criteria will be applicable to the new diagnostic entity. Another major change is the use of operational criteria to define premature ejaculation as an ejaculatory latency of approximately 1 minute or less. This definition is analogous to the definition adopted by the International Society of Sexual Medicine (McMahon et al., 2008). It is possible that the efficacy of various treatment approaches for premature ejaculation may vary depending on the length of the ejaculatory latency period.

The *DSM-5* criteria have been criticized on multiple grounds. The major focus of concern appears to be changes in criteria for sexual disorders in women. Some have questioned whether there are sufficient data to justify "merging" HSDD and female sexual arousal disorder within the new entity of female sexual/interest/arousal disorder (Clayton et al., 2012; Derogatis, 2010; Fabre & Smith, 2010). Others have raised similar concerns about the merger of dyspareunia and vaginismus into one entity, GPPD (Laan et al., 2010). There has also been criticism that there are insufficient data to warrant a criterion of 60 seconds or less for premature ejaculation (Jern, 2010; Rubio-Aurioles, 2010) and the duration and frequency criteria for ED (Eardley, 2010; Nelson, 2010). The *DSM-5* task force on sexual dysfunctions addressed these criticisms (Binik et al., 2010), suggesting that all changes to criterion sets were based on empirical findings.

EPIDEMIOLOGY

The largest study of the prevalence of sexual concerns in the United States, conducted by Laumann and colleagues (1999), is known as the National Health Social Life Survey. This survey was a probability sample of U.S. adults, aged 18 to 59. The sample consisted of 2,968 adults. All were interviewed face to face with a structured interview. Sexual problems were more prevalent among women than men. Among males, the most common problems were difficulty with orgasm (8.3%), lack of interest (15.8%), rapid ejaculation (28.8%), and erectile difficulties (9.8%). Erectile difficulties were positively correlated with age. Women complained of painful coitus (14.4%), lack of interest (33.4%), inability to reach orgasm (24.1%), and difficulty with lubrication (18.8%). Feldman and colleagues (1994) studied the epidemiology of ED and its medical and psychosocial correlates in a random sample of men aged 40 to 70 who lived in cities and towns near Boston. A self-administered sexual questionnaire was used. Approximately half of the population reported at least occasional problems with erections. The prevalence of erectile problems was highly correlated with age: Only 5% of men aged 40 reported total erectile failure as compared with 15% of men aged 70. Other variables associated with erectile failure were depressive symptoms, cigarette smoking, heart disease, and hypertension. A prospective study of the same sample found that the incidence of impotence was related to various cardiovascular risk factors, as well as a submissive personality (Araujo et al., 2000;

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 non-vaginal sexual activities, specific duration criteria have not been established for these activities)
B. The symptom in Criterion A must have been present for at least 6 months and 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)

Genito-pelvic pain/penetration disorder

A. Persistent or recurrent difficulties with one or more of the following:
   1. Having vaginal intercourse/penetration
   2. Marked vulvovaginal or pelvic pain during vaginal intercourse
   3. Marked fear or anxiety either 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
B. The symptoms in criterion A have persisted for a minimum duration of approximately 6 months

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, or absence of orgasm
   2. Markedly reduced intensity of orgasmic sensation
B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months

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 activities
   2. Absent/reduced sexual/erotic thought or fantasies
   3. No/reduced initiation of sexual activity, and typically unresponsive to a partner's attempts to initiate
   4. Absent/reduced sexual excitement/pleasure during sexual activity on all or almost all (approximately 75–100%) sexual encounters (in identified situational contexts 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, etc.)
   6. Absent/reduced genital and/or non-genital sensations during sexual activity on almost all or all (approximately 75–100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts)
B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months

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
   2. Marked difficulty in maintaining an erection until the completion of sexual activity
   3. Marked decrease in erectile rigidity
B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months

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
B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months

(*continued*)

BOX 22.2 (continued)

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 context of the individual's life.
B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months

Substance/medication-induced sexual dysfunction

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 finding 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

Note: For all disorders except substance/medication-induced sexual dysfunction, Criterion C and D are as follows: Criterion C. The symptoms in Criteria A cause clinically significant distress in the individual; Criterion D. The sexual dysfunction is not better explained by a non-sexual mental disorder or as a consequence or severe relationship distress or other significant stressors, and is not attributable to the effects of substance/medication or another medical condition.

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BOX 22.3 Additional Specifications in *DSM-5*

*Specify whether**:
Lifelong: the disturbance has been present since the individual became sexually active
Acquired: the disturbance began after a period of relatively normal sexual function

*Specify whether**:
Generalized: not limited to certain types of stimulation, situations, or partners
Situational: only occurs with certain types of stimulation, situations, or partners

*Specify current severity***

Mild: evidence of mild distress over the symptoms in Criterion A
Moderate: evidence of moderate distress over the symptoms in Criterion A
Severe: evidence of severe distress over the symptoms in Criterion A

*These specifications are required for all of the sexual dysfunctions except substance/medication-induced sexual dysfunction.

**Severity specification in not required for substance/medication-induced sexual dysfunction.

The severity specification for premature (early) ejaculation differs from that of the other sexual dysfunctions is as follows: (1) Mild: ejaculation occurring within approximately 30 seconds to 1 minute of vaginal penetration; (2) Moderate: ejaculation occurring within approximately 15–30 seconds of vaginal penetration; (3) Severe: ejaculation occurring prior to sexual activity, at the start of sexual activity, or within approximately 15 seconds of vaginal penetration.

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BOX 22.4 Changes in *DSM-5* from *DSM-IV-TR*

1. Requirement that each of the dysfunctions causes clinically significant distress in the individual
2. Requirement that most of the sexual disorders be present on 75% or more of occasions and have been present for approximately 6 months or longer
3. Specification of an intravaginal latency time criterion for premature ejaculation
4. Inclusion of severity ratings
4. Deletion of etiological specification (subtype)
4. Deletion of sexual aversion disorder, female arousal disorder, vaginismus, dyspareunia, and sexual dysfunction due to a general medical disorder
5. Male orgasmic disorder, premature ejaculation, and substance-induced sexual dysfunction diagnoses changed to delayed ejaculation, premature (early) ejaculation, and substance/medication-induced sexual dysfunction
6. Changed hypoactive sexual desire disorder to apply only to males
7. Addition of genito-pelvic pain/penetration disorder and female sexual interest/arousal disorder

Johannes et al., 2000). Pinnock, Stapleton, and Marshall (1999) used a mailed questionnaire to study the prevalence of erectile problems in a probability sample of men over 40 in South Australia. ED was correlated with age: Only 3% of men aged 40 to 49 reported erections insufficient for coitus, compared with 64% of men aged 70 to 79. Various cardiovascular risk factors were associated with the presence of ED. Similar studies of the prevalence of ED have taken place in Thailand, Malaysia, Japan, and Italy (Parazzini et al., 2000; Shirai et al., 1999). In these studies, increasing age and cardiovascular risk factors were associated with ED. Hawton, Gath, and Day (1994) studied a community sample of middle-aged women in the Oxford area in the United Kingdom. A semistructured interview was used. Questions concerned sexual and orgasm frequency. Marital adjustment was the main predictor of sexual activity and satisfaction. In this sample, 17% of participants stated that they experienced orgasm on all coital opportunities, 16% said they never experienced orgasm, and 29% said they experienced orgasm more than 50% of the time. Two percent said they never enjoyed coitus, whereas 41% said they always enjoyed coitus. Dunn, Croft, and Hackett (1999) sent an anonymous postal questionnaire to a stratified random sample of the adult general population in the United Kingdom. More women than men had sexual problems. The most common sexual problems in women were vaginal dryness and infrequent orgasm.

A global study of the prevalence of sexual disorders surveyed 27,500 subjects from 29 countries (Laumann et al., 2005). In women the most common difficulties were lack of interest (26% to 43%), inability to reach orgasm (18% to 41%), and difficulty with lubrication (31%). In men, the most common difficulties were rapid ejaculation (24%) and erectile problems (17%). Most difficulties were more prevalent in eastern and southeastern Asia than in other parts of the world. The significance of regional differences in prevalence proved difficult to determine because different response rates and inquiry techniques were used in different countries. Despite the high prevalence of sexual problems, it is interesting that less than 18% of subjects requested help with their difficulty, and only 9% reported being asked about sexual problems by their physicians (Moreira et al., 2005). A critical review of current epidemiological research concerning sexual difficulties was recently published (Lewis et al., 2010).

Although there have been numerous studies of the prevalence of sexual concerns, the true prevalence of sexual dysfunction as defined by the *DSM-IV-TR* and *DSM-5* is unclear. The prevalence of problems meeting diagnostic criteria is much less than the studies mentioned above. King and colleagues (2007) studied the prevalence of sexual dysfunction in consecutive attendees to general practices in London. Thirty-eight percent of women received an ICD-10 diagnosis of sexual dysfunction. However, only 18% of those so diagnosed agreed that they had a problem. Most women attributed their change in sexual responsiveness to relationship and emotional difficulties. Similarly, Dennerstein and colleagues (2008), in a prospective study of Australian women, found that most aspects of sexual function declined markedly during menopause transition; however, only a minority were significantly distressed by this change in sexual function. A probability sample of 11,161 British men and women aged 16 to 44 found that sexual problems lasting 1 month or less were far more common than those lasting at least 6 months (Mercer et al., 2003). For example, 40% of the women reported problems with lack of interest in sex the previous year; however, only 10% complained of this problem lasting at least 6 months. Similarly, 5.8% of the men complained of difficulty achieving an erection, but only 0.8% complained of erectile problems lasting 6 months. In the Global Study of Sexual Problems (Laumann et al., 2005), reports of frequent problems with sexual concerns were far less common than occasional problems. For example, approximately 13% of men in Northern Europe complained of erectile problems, but less than 3% indicated that this was a frequent problem. Similar differences in prevalence according to frequency of occurrence were reported for other sexual difficulties in differing regions of the world. Surveys have reported that 28% to 30% of men complain of premature ejaculation. Studies using time estimates have found that the prevalence of men with ejaculatory latencies of 1 minute or less is less than 3% (Park et al., 2010; Serefoglu et al., 2011; Waldinger et al., 2009).

Some sexual dysfunctions may be associated with other Axis I disorders. For example, mood disorder may be associated with an increased prevalence of HSDD and male ED (Kennedy et al., 1999; Thase et al., 1999). Euthymic patients with a current diagnosis of HSDD have an increased lifetime prevalence of mood disorder (Schreiner-Engel &

Schiavi, 1986). There are also reports of decreased libido being more common in patients with schizophrenia (Aizenberg et al., 1995), anorexia nervosa (Raboch & Faltus, 1991), and anxiety disorders (Minnen & Kampman, 2000). Erectile problems appear to be common in men with posttraumatic stress disorder (Congrove et al., 2002), and patients with obsessive-compulsive disorder have been found to have multiple sexual problems, including difficulty reaching orgasm (Fontelle et al., 2007) Comorbidity between anxiety disorders including social anxiety and premature ejaculation have been found (Corretti et al., 2006; Figueira et al., 2001). However, most cases of sexual dysfunction do not have a clear relationship to another Axis I disorder. There also is minimal evidence of a relationship between sexual dysfunction and personality disorder (Segraves, 1989). Personality traits of introversion, emotional instability, and not being open to new experiences have been found to be associated with decreased orgasmic capacity. Most clinicians assume that the immediate causes of sexual dysfunction involve anxiety about performance, a cycle of demand and negative expectancies, and self-defeating cognitions (Segraves, 1989).

WHAT CONSTITUTES A SUCCESSFUL INTERVENTION?

Human sexual behavior involves a complex interplay of individual, interpersonal, cultural, and biological factors. Typically, outcome studies of biological interventions, such as the use of PDE5 inhibitors for the treatment of ED, have focused on the restoration of genital function as the primary outcome measure. Patient satisfaction and effects on interpersonal interaction are also frequently assessed and, most often, restoration of genital function has had a positive influence on both individual and interpersonal psychological factors (Seftel et al., 2009). However, since genital function has personal and interpersonal symbolic significance, this is not always the case (Wise, 1999). There is increasing evidence that interventions that focus on psychological as well as biological factors have more favorable outcomes (Althof, 1995a).

Studies of psychological interventions are difficult to design and conduct. The challenge is to design methodologically sound studies that also reflect the complexity of individual variation and are acceptable to patients. For example, many patients may not agree to be in a waitlist control group, and for those who initially agreed to be in a waitlist control group, attrition may limit a meaningful comparison of treatment versus no treatment. In pharmacological studies, one can include a placebo treatment. In psychological interventions, the inclusion of a plausible placebo treatment is extremely difficult, as both the therapist and the patient will need to believe that it is a legitimate therapy. In psychological therapies, it is also difficult to control for therapist effects: The "same" therapy delivered by two different therapists may have different outcomes.

METHODOLOGICAL PROBLEMS IN SEX THERAPY OUTCOME STUDIES

Initial studies of outcomes of psychological treatment of sexual dysfunction were criticized because they had small sample sizes, did not use experimental control groups (waitlist, alternative treatment groups), lacked random allocation to treatment, failed to provide clear-cut criteria for admission into the study, lacked long-term follow-up, and inadequately described the intervention (Spence, 1991). Some of these criticisms apply to more recent studies.

Other problems with studies of psychological interventions include the possible contamination of the study population. This is apparent in early studies of the treatment of ED, in which men whose problems had organic etiologies were incorrectly diagnosed as having psychogenic ED. Clearly, psychological interventions alone were unlikely to benefit men whose erectile problems were caused by vascular disease. Thus, these outcome studies may have been biased in a negative direction. The same may be true of current studies of psychotherapy for other sexual disorders. For example, it is likely that some of the women currently being treated psychologically for desire/arousal problems have idiopathic disorders that may subsequently be found to have biological etiologies.

PSYCHOLOGICAL TREATMENTS OF SEXUAL DYSFUNCTION: GENERAL FORMULATIONS

Masters and Johnson (1970) introduced an intensive outpatient model of sex therapy involving daily combinations of individual and couple psychotherapy,

administered by a mixed-sex co-therapy team. Their treatment model was impractical in most settings. Subsequently, therapists modified the approach to involve weekly sessions and a single therapist. Early studies found that a single therapist had similar outcomes to a mixed-sex co-therapy team and that a therapist of the same sex as the patient was not required.

Subsequent research (Hawton, 1995) identified the following variables associated with positive outcomes from psychological interventions:

1. The quality of the couple's general relationship, particularly the female partner's general assessment of the relationship (Hawton & Catalan, 1986);
2. The motivation of the partners, particularly the male partner, for treatment (Hawton & Fagg, 1991; Stephenson Rellini, & Meston, 2013);
3. Absence of serious psychiatric disorder in either partner;
4. Physical attraction between the partners;
5. Early compliance with treatment program homework assignments.

Other research studied the efficacy of individual versus group psychotherapy approaches and found minimal evidence to support one approach over the other (Duterte et al., 2007). However, the vast majority of patients preferred individual or couple therapy and not group therapy.

A limited number of more recent studies have employed waitlist controls. Studies have also investigated combined psychological and pharmacological therapy and use of the Internet to deliver psychotherapy (Althof, 2010). Psychotherapy has shifted to a cognitive-behavioral model with clear specification of different components of intervention. However, there have been very few studies investigating the individual contribution of these different treatment components.

OUTCOMES OF TREATMENTS FOR SPECIFIC SEXUAL DYSFUNCTIONS

Male Hypoactive Sexual Desire Disorder

Men report problems with desire far less frequently than women (Laumann et al., 1999), and there is minimal information available concerning the psychological treatment of desire problems in men. The major issue in treatment decision making is a careful differential diagnosis to identify etiologies with established interventions. In general, a presentation of a lifelong problem of low sexual desire or a situational pattern to the problem is suggestive of a psychological etiology. Syndromes to be considered in the differential diagnosis of acquired male HSDD include untreated depression, drug side effects, and endocrinopathies such as hypogonadism, hypothyroidism, or hyperprolactinemia (Segraves, 2008). As stated above, there is minimal evidence regarding the efficacy of psychological therapies for HSDD in men. Cognitive-behavioral treatment approaches involve helping the man to develop sensory awareness and to identify erotic cues, desensitization of anxiety, and cognitive restructuring (LoPiccolo & Friedman, 1988). Psychoanalytic approaches concentrate on the transference relationship and the internalization of exciting and rejecting objects. The only evidence supporting any of these psychological approaches consists of case reports or small clinical series.

Double-blind studies have shown that successful treatment of depression can restore libido unless the psychopharmacological agent itself has sexual side effects (Labbate, 2008). Drug side effects should be considered if the problem occurs shortly after drug initiation or dose increase. Clinical studies indicate that the addition or substitution of bupropion for an serotonergic antidepressant may alleviate selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction (Balon, 2009). Clinical series have also suggested that the substitution of aripiprazole for prolactin-elevating antipsychotic drugs may alleviate antipsychotic drug-induced sexual dysfunction (Nunes et al., 2012).

The relationship between serum testosterone and libido within normal ranges is unclear. However, controlled trials and large clinical series have established that exogenous testosterone supplementation can restore libido in hypogonadal men (Maurice, 1999). Clinical series have shown that the use of prolactin-lowering drugs can restore sexual desire in men with frank prolactinemia. Data from clinical series indicate that thyroid hormone therapy in men with hypothyroidism may normalize libido (Maggi et al., 2013).

Female Sexual Interest/Arousal Disorder

As discussed earlier, female sexual interest/arousal disorder is a new diagnostic code in *DSM-5* that

combines elements of HSDD in *DSM-IV-TR* with elements of subjective arousal. There are strong reasons to expect that research done using HSDD criteria will be applicable to the new entity. These reasons include the following: (1) high comorbidity between measures of sexual arousal and sexual desire; (2) the finding that most women don't distinguish between desire and arousal; and (3) the fact that pharmacological interventions that affect measures of desire also affect arousal (Buster et al., 2005).

Psychological Therapies

There have been a limited number of controlled studies of the psychotherapy of HSDD in females. Most studies employed a variant of CBT administered in a group format. Some studies have attempted to decipher the efficacy of specific components of therapy. The evidence concerning the efficacy of psychotherapy of sexual disorders has been recently reviewed elsewhere (Gunzler & Berner, 2012; Ter Kuile et al., 2010). Trudel and colleagues (2001) reported a study of the efficacy of multimodal CBT for women meeting operational diagnostic criteria for HSDD in *DSM-IV-TR*. The criteria used indicate that the women in his study also met criteria for female sexual interest/arousal disorder as defined in *DSM-5*. The women were found to have various irrational, negative automatic thoughts, core irrational beliefs, antisexual attitudes, anticipatory anxiety, fears of abandonment, and corresponding negative affects before treatment. Thirty-eight couples were randomly assigned to CBT consisting of 12 weekly, 2-hour group couple therapy sessions and 36 couples to a 12-week waitlist control group. Seventy-four percent of women in treatment were improved or cured at the end of treatment, a gain that was largely maintained at the 3-month and 1-year follow-ups. At the end of treatment, 28% of the women considered themselves totally cured. Similar results were found on multiple questionnaire variables on which the treatment group demonstrated significant positive changes in comparison to the waitlist control group. Hurlbert and Apt (1995) compared the efficacy of a CBT approach administered in women-only group therapy versus in couples-only group therapy versus a waitlist control group for the treatment of HSDD in women. Nineteen patients were in each group. The treatment approach consisted of a multimodal treatment package augmented by orgasm consistency training. A previous study by Hurlbert (1993) had demonstrated the efficacy of orgasm consistency training in women with HSDD. Orgasm consistency training consists of teaching the male partner to delay ejaculation, directed masturbation exercises for the female, directing couples that the female should reach orgasm first ("the ladies come first rule"), and directing the man to shift forward during thrusting so that there is more clitoral contact during coitus ("the coital alignment technique"). Both treatment groups demonstrated significant improvement in comparison to the waitlist control group, and the couples-only group demonstrated greater improvement than the women-only group approach.

Other promising approaches include Internet-based therapies (Jones & McCabe, 2011) and approaches based on mindfulness (Brotto et al., 2008a, 2008b). To date, there are no controlled data comparing either of these interventions to a control condition in women diagnosed with either HSDD or female sexual interest/arousal disorder. Mindfulness is an approach that emphasizes present-moment nonjudgmental awareness.

Pharmacotherapy

No agents have been approved by the FDA for the treatment of desire disorders in women, although there is considerable interest in the role of testosterone in female libido. Abnormally low endogenous androgen levels have been proposed as one etiology for HSDD in females. In premenopausal women, testosterone is derived from the ovaries and adrenal glands. There is a gradual decline in serum testosterone with aging and a dramatic decline after oophorectomy. Studies have not found a consistent relationship between serum testosterone and sexual function in women (Davis, Davison, Donath, & Bell, 2005; Dennerstein, Dudley, Hopper, & Burger, 1997). Several factors may explain the lack of a correlation between testosterone levels and sexual function in women. Blood levels of testosterone may not reflect tissue concentrations as there is considerable intracellular metabolism of testosterone, and accurate measurement of testosterone at the levels present in women is difficult (Fooladi & Davis, 2012). As of 2010, there had been 35 double-blind controlled trials involving 4,768 women of adding testosterone to

conventional postmenopausal hormone therapy. The available evidence clearly indicates that adding testosterone to hormone therapy improves sexual function, measures of interest in sexual activity, and the number of satisfying sexual events (Somboonporn et al., 2010). Most of these studies involved study of the effects of adding transdermal testosterone to hormone replacement in postmenopausal women, although there is some evidence for a beneficial effect of transdermal testosterone in older premenopausal women (Davis et al., 2008). Other forms of delivery such as creams and gels have also been studied. The efficacy of testosterone cream in women has been demonstrated (El-Hage et al., 2007), whereas there have been inconsistent data concerning the efficacy of testosterone gel (Fooladi & Davis, 2012). Studies of dehydroepiandrosterone have not found significant effects on sexual desire. Similarly, studies of peripheral vasodilators such as sildenafil have not shown efficacy in the treatment of HSDD (Al-Azzawi et al., 2009).

The link between postmenopausal estrogen-progesterone therapy and breast cancer has led to concern about any form of hormone therapy. Safety data from controlled double-blind studies of transdermal testosterone suggest that there are no significant health risks in up to 2 years of therapy. As a consequence, off-label use in women of transdermal testosterone formulated for men is common in the United States. Whether there are health risks with the use of testosterone beyond 2 years is unknown.

A single-blind study found that bupropion increased various indices of libido in women with hypoactive sexual desire disorder (Segraves et al., 2001); a subsequent double-blind study found that bupropion had significant effects on questionnaire measures of sexual arousal, orgasm, and satisfaction (Segraves, Clayton, & Croft, 2004).

Other compounds are being investigated for the treatment of desire problems in women. These include flibanserin and melanocyte-stimulating hormone analogues. A preparation of testosterone combined with a PDE inhibitor is also being studied.

Erectile Disorder

Psychological Intervention

Two recent reviews of controlled studies of psychosocial interventions for ED have concluded that there is evidence that psychosocial interventions are superior to waitlist control groups and that the combination of psychosocial therapy and oral pharmacotherapy is superior to oral pharmacotherapy alone (Berner & Gunzler, 2012; Melnik et al., 2008). The available evidence consists of studies of varying quality using differing therapeutic approaches. For example, therapeutic approaches have included creative-dynamic image synthesis (Sommer et al., 2001), virtual reality methods (Optale et al., 1997), hypnotic suggestion (Aydin et al., 1997), theme-based psychotherapy (Melnik & Abdo, 2005), and CBT approaches (Andersson et al., 2011; McCabe, 2001). Differing outcome measures have been used, and some studies used such small sample sizes that one would not expect to find differences between treatment approaches. For example, one study compared five conditions, each of which included only four men (Kilmann et al., 1987). Two studies have found evidence that CBT is superior to a waitlist control group (Andersson et al., 2011; McCabe, 2001). One study did not find an advantage to combining counseling with intracavernosal injection therapy (van der Windt et al., 2002), and one study did not find a significant benefit from adding counseling to vacuum erection device therapy (Wylie et al., 2003).Three studies found that counseling combined with sildenafil therapy was superior to sildenafil therapy alone (Abdo et al., 2008; Banner & Anderson, 2007; Melnik et al., 2012; Phelps et al., 2004). One study actually found counseling to be more effective than oral sildenafil therapy (Melnik & Abdo, 2005).

Pharmacotherapy

Clearly, the most acceptable pharmacotherapy for ED is an oral medication. The introduction of the oral agent sildenafil in 1998 had a dramatic effect on the treatment of erectile problems (Goldstein et al., 1998). At this point, oral PDE inhibitors (e.g., sildenafil, vardenafil, tadalafil, and avanafil) are first-line therapies for ED. These drugs are intracellular signal amplifiers and slow the degradation of cyclic guanosine monophosphate, thus leading to a chain of events resulting in decreased intracellular calcium, relaxation of the smooth muscle of the corpus cavernosum, and thus penile erection (Tsertsvadze et al., 2009). These drugs thus enhance the ability of a man to achieve an erection given adequate psychological or physical stimulation. They do not

produce spontaneous erections or enhance libido. The efficacy of the PDE inhibitors has been demonstrated in multiple double-blind, placebo-controlled, multicenter type 1 studies (Osterloh, Eardley, Carson, & Padma-Nathan, 1999). There have been 72 parallel-group, placebo-controlled studies of sildenafil, 27 involving vardenafil and 28 involving tadalafil. Avanafil was recently introduced in the U.S. market (Goldstein et al., 2012). In all of these studies, there was a significant difference between the PDE inhibitor and placebo in the ability to obtain erections sufficient for penetration and the ability to maintain them after penetration. Increasing doses of drug were associated with increased erectile function. Scientifically sound studies have been conducted in men with hypertension, including those currently receiving medications for their disease, and the drug has also been shown to be helpful to men with type 1 and type 2 diabetes (Vardi & Nini, 2009), spinal cord injury, postradical prostatectomy (Candy et al., 2008), and depression (Albersen et al., 2012). Depending on the etiology of the dysfunction, efficacy ranges between 40% and 80%. All of the PDE5 inhibitors appear to have similar efficacy and a similar side-effect profile (Yuan et al., 2008). The primary difference between these compounds appears to be that tadalafil has a longer duration of action.

The most common side effects include headache and facial flushing, seen in 10% to 20% of men; dyspepsia, seen in 5% of men; and red/blue color vision changes or blurry vision, seen in 3% of men. The headache and facial flushing may be explained by the vasodilatory effects of sildenafil on the cerebral circulation. The dyspepsia is due to the small overlap in sildenafil activity with type 4 PDE found at the gastroesophageal sphincter, leaving the gastroesophageal sphincter open. All of the PDE inhibitors have mild effects on PDE5 located in the rod and cone photoreceptors and can cause mild reversible visual symptoms. There have also been reports of ischemic optic neuropathy associated with PDE5 use, although a causal relationship has not been established (Kerr & Danesh-Meyer, 2009).

Absolute contraindications to sildenafil use are the concomitant use of nitrate drugs. Caution has been advised in patients with retinitis pigmentosa, preexisting hypotension, and the use of multiple antihypertensive agents (American College of Cardiology and American Heart Association Consensus Group, 1999; Tomlinson, 1999). The significance of cardiac deaths is difficult to evaluate because the majority of men taking sildenafil have cardiovascular risk factors. A small number of cases of priapism have been reported with sildenafil. The primary action of sildenafil is peripheral.

Prior to sildenafil the only other oral agent for ED was yohimbine, a natural herb of an African tree bark. Yohimbine is an alpha-2 adrenergic antagonist (Morales, Surridge, & Marshall, 1987). Double-blind studies have shown that it has modest efficacy, mainly in men with psychogenic erectile problems (Reid et al., 1987; Riley, Goodman, Kellet, & Orr, 1989; Sondra, Mazo, Segraves, & Chanceler, 1990; Susset et al., 1989). There are few objective, placebo-controlled studies that validate the efficacy of yohimbine.

Three separate double-blind trials have established that subcutaneous apomorphine is effective in eliciting erections approximately 20 minutes after administration (Danjou, Alexander, Warat, Combiez, & Perch, 1988; Lal, Ackman, Thavundayil, Kieley, & Etienne, 1984; Segraves, Bari, Segraves, & Spirnak, 1991). It has been hypothesized that apomorphine acts at the level of the paraventricular nucleus of the brain (Chen, Chan, & Chang, 1999). Early data suggest a significant improvement in erectile activity over placebo (Heaton, Morales, Adams, Johnston, & el-Rashidy, 1999; Mulhall & Goldstein, 1999). The clinical utility of both subcutaneous and sublingual apomorphine has been limited by its propensity to cause nausea. Apomorphine has less efficacy than the PDE5 inhibitors and is not available in the U.S. market (Eardley, Wright, MacDonagh, Hole, & Edwards, 2004; Gontero et al., 2005; Perimenis et al., 2004).

Other pharmacotherapies for ED include transurethral systems (MUSE) and intracorporeal injection therapy. Both these methods employ different delivery systems to introduce vasoactive substances into the corpora cavernosa of the penis. Of the two approaches, intracavernosal injection therapy has a higher success rate in producing firm erections. The parameters of such therapy, dose regimens, and side effects are well established. The efficacy for psychogenic as well as organic erectile problems appears well established (Althof et al., 1991). The three most common agents used to induce erections are papaverine hydrochloride, phentolamine, and prostaglandin E1. Although they are frequently combined, each agent can be used singly (Althof & Seftel, 1995). As one might expect, there have also been a number

of reports and studies employing the triple therapy of papaverine, phentolamine, and prostaglandin El, referred to as tri-mix (Barada & McKimmy, 1994). Triple therapy appears to have superior results over the use of papaverine phentolamine combination therapy for some conditions, such as severe arteriogenic disease (McMahon, 1991). Triple therapy has also been used in patients with psychogenic impotence (Bennett, Carpenter, & Barada, 1991). Papaverine and papaverine-phentolamine injection therapy have the disadvantages of causing delayed corporeal fibrosis, variable efficacy, systemic reactions, and the risk of prolonged erections (Levine et al., 1989).

Vacuum Tumescence Devices

An alternative strategy for the man who is resistant to trying or has not benefited from psychotherapy and who finds the concept of self-injection of a substance into the penis somewhat aversive is the use of the external vacuum erection device. The vacuum device is placed over the penis, and a negative pressure facilitates blood flow into the penis, producing an erection. A tension ring (rubber band) is slipped from the base of the vacuum erection device to the base of the penis, maintaining the erection. Different studies using diverse patient populations have reported that between 70% and 100% of men will achieve erections using this device (Althof & Seftel, 1995; Turner, Althof, & Levine, 1992). Dropout rates are around 20%. Side effects are minimal, and there is no evidence of significant negative psychological effects from employing this device. However, with the introduction of effective oral erectogenic agents, the use of mechanical aids has decreased.

Premature Ejaculation

The behavioral treatment for premature ejaculation was first described by a urologist, James Semans, in 1956. He reported a high success rate using a technique that involved having the female stimulate her partner's penis until just before the point of ejaculatory inevitability, stopping, and then restarting stimulation. This intervention is repeated until the man can voluntarily delay ejaculation. Masters and Johnson (1970) reported a similar technique using a firm frenulum squeeze prior to the point of ejaculatory inevitability. Once control is achieved with manual stimulation, the couple is instructed to have coitus using the female-superior position. Again, the male is instructed to signal just prior to ejaculatory inevitability, at which point the partner ceases movement. Once he indicates that he has regained control, she begins movement again. Most contemporary clinicians employ either the start/stop or frenulum-squeeze technique as part of their treatment of premature ejaculation (Maurice, 1999; Metz & McCarthy, 2003; Rowland & Cooper, 2011). Despite the widespread adoption of this technique, there is limited evidence supporting the efficacy of the psychological treatment of premature ejaculation (Melnik et al., 2011).

One major controlled study demonstrating the efficacy of behavioral treatment of premature ejaculation was reported by DeCarufel and Trudel in 2006. This study reported that both behavioral therapy and a cognitive therapy approach in which men were taught to recognize various levels of sexual excitement were superior to a waitlist control group. Outcome measures included measurement of ejaculatory latency, sexual satisfaction, and questionnaire measures of sexual interaction. Gains were maintained at a 3-month follow-up evaluation. Three other controlled studies compared the efficacy of psychological interventions to pharmacotherapy (Abdel-Hamid et al., 2001; Li et al., 2007; Yuan et al., 2008). These studies produced mixed results. One study found that counseling plus chlorprazine was superior to drug alone (Li et al., 2007), while another study found behavior therapy to be similar in outcome to SSRI therapy (Abdel-Hamid et al., 2001).

Pharmacological Treatments

A large number of placebo-controlled, double-blind studies have demonstrated that daily treatment with fluoxetine, sertraline, clomipramine, and paroxetine can be used to delay ejaculatory latency in men with rapid ejaculation. Consistent findings have been obtained using a variety of outcome measures, including patient estimate of time between penetration and ejaculation, partner estimate, and patient or partner report of stopwatch readings. It appears that ejaculatory delay occurs only during active drug treatment and that sustained pharmacotherapy is necessary for most men to maintain a slower pattern of ejaculation. The effect is usually reported after 1 to 2 weeks of treatment. Chronic treatment with 20 to 40 mg of

paroxetine (Waldinger, Hengeveld, & Zwindman, 1994, 1997), 25 to 50 mg of clomipramine (Althof et al., 1995; Kim & Seo, 1998), 50 to 200 mg of sertraline (Biri et al., 1998; Kim & Seo, 1998; McMahon, 1998a, 1998b; Mendels, Cameram, & Sikes, 1995), or 20 mg of fluoxetine (Haensel, Klem, Hop, & Slo, 1998; Kara et al., 1996) has been shown to increase ejaculatory control in men experiencing rapid ejaculation (Giuliano & Clement, 2012). A meta-analysis of the published data indicates that paroxetine has a stronger effect in promoting ejaculatory delay than the other SSRIs (Waldinger, 2003).The effect of these drugs on ejaculatory latency dissipates when the drug is discontinued.

Some investigators have investigated the efficacy of various drugs taken as needed. The available evidence indicates that clomipramine, a serotonergic antidepressant, can be effective when taken on an as-needed basis; five double-blind controlled studies have reported these findings. Dosing is typically 25 to 50 mg taken approximately 5 hours prior to coitus. Ejaculatory latency has been reported to increase fourfold (Althof et al., 1995; Haensel & *Rowland* 1996; Segraves et al., 1993; Strassberg et al., 1999: Waldinger, 2007).

Several investigators have explored the use of SSRIs when on-demand therapy is preceded by daily treatment (Kim & Paick, 1999; McMahon & Touma, 1999). The data concerning this approach are mixed.

Dapoxetine, a serotonin reuptake inhibitor, has been studied in over 6,000 subjects and been approved for use in the treatment of premature ejaculation in many countries (although not the United States). Dapoxetine hydrocholoride is a short-acting SSRI characterized by rapid absorption and clearance. It is effective when used on demand and has been shown to be effective in men with lifelong as well as acquired premature ejaculation.

Topical anesthetic creams and sprays have also been shown to be effective in delaying ejaculation. Prilocaine-lidocaine formulations have been demonstrated to be effective (Atikeler et al., 2002; Basuto & Galindo, 2004; Berkovich et al., 1995; Dinsmore & Wyllie, 2009; Henry & Morales, 2003). Another approach is the use of creams formulated from plant products. For example, SS-cream, formulated from nine natural products, is applied to the penis 1 hour prior to coitus (Xin et al., 2000). Placebo-controlled, double-blind studies have demonstrated that this compound increases ejaculatory latency (Choi et al., 2000; Xin et al., 2000).

There have been reports that sildenafil may help in the treatment of rapid ejaculation (Chen et al., 2003: Salonia et al., 2002). However, a recent controlled study did not find evidence of efficacy of sildenafil in the treatment of premature ejaculation (McMahon et al., 2005, 2006).

Double-blind placebo-controlled studies have also found that tramadol, a mild opioid receptor agonist, can be effective in delaying ejaculation when taken on demand (Bar-Or et al., 2012; Giuliano, 2007; Salem et al., 2008). This strategy would not be recommended as a first-line therapy because of the potential of addiction with this agent.

Delayed Ejaculation

Because delayed ejaculation is one of the least commonly encountered sexual complaints in clinical practice, there is a paucity of information concerning its etiology and treatment. *DSM-5* does specify clear criteria regarding when this diagnosis should be made. It has been suggested that this diagnosis should definitely be considered in men who are unable to ejaculate after 25 to 30 minutes of sexual activity and are distressed by their inability to ejaculate sooner. Some men will simply cease sexual activity after shorter time periods because of pain and/or exhaustion (McMahon et al., 2013). The *DSM-5* recommends that the subtypes "lifelong versus acquired" and "situational versus global" be used. It has also been suggested that psychogenic etiologies be given primary consideration in cases of lifelong premature ejaculation and that organic etiologies should receive primary consideration in acquired delayed ejaculation. Similarly, psychological factors would be strongly considered when the man reports a situational pattern to his failure to ejaculate (i.e., able to ejaculate with one partner and not another) and that organic factors would be more likely in cases of acquired delayed ejaculation. Although these suggestions have face validity, there is limited empirical evidence to support these assumptions (Segraves, 2010a).

No controlled trials of psychological treatment of delayed ejaculation have been reported. Psychological treatment appears to vary mainly by the theoretical orientation of the psychotherapist. Psychoanalytically oriented therapists posit that

insight-oriented psychotherapy focusing on becoming aware of unconscious motivation (e.g., fear or anger at the partner) is the preferred intervention. Therapists with a cognitive-behavioral orientation have noted that many men with delayed ejaculation have a vigorous masturbatory style that produces much more stimulation than vaginal penetration (Perelman, 2005a,b) or have sexual fantasies during masturbation that are more arousing than sex with the partner. Interventions include vibrator stimulation, more vigorous penile thrusting, masturbatory retraining, encouraging the partner to stimulate the patient's penis vigorously during foreplay, and realigning sexual fantasies (Althof, 2012; Rowland et al., 2010). Although many of the case reports of delayed ejaculation are compelling, there are no controlled trials using any of these methods.

No pharmacological agents are approved for the treatment of delayed ejaculation. Moreover, there are no controlled double-blind studies of the efficacy of any pharmacological therapy for delayed ejaculation (McMahon et al., 2013; Waldinger & Schweitzer, 2005). Case reports suggest that drugs with dopaminergic or adrenergic activity such as amantadine, cabergoline, pseudoephrine, reboxetine, bupropion, and yohimbine may benefit some cases. There have also been case reports reporting success with oxytocin, buspirone, and cyproheptadine.

Female Orgasmic Disorder

Spence (1991) presents a cogent summary of the dilemmas to be considered in assessing the efficacy of therapy for women with orgasmic disorders. The primary issue remains unresolved: Is success predicated solely on coital orgasm, on partnered sexual activity with orgasm through any means, or by orgasm achieved by masturbation? Most contemporary therapists would consider orgasm by any means in a partnered relationship to be a treatment success, although many patients prefer orgasm during coitus. This expectation may be reinforced by the partner. Adding to the confusion is the media's constant reinforcement of unrealistic expectations from sexual encounters. Both men and women are led to believe that all women can easily and regularly achieve orgasm from intercourse alone.

Recent research indicates that orgasmic capacity has a genetic component (Dunn et al., 2005) and is related to certain normal personality traits (Harris et al., 2008). Other research indicates that (1) only about 25% of women report regularly achieving orgasm during partnered sexual activity (Lloyd, 2005); (2) many women are not distressed by absence of orgasm during sexual activity (King et al., 2007); (3) women vary widely in the type of stimulation that triggers orgasm (Meston et al., 2004); (4) orgasmic difficulties are often comorbid with anxiety, depression, and relationship difficulties (Rellini & Clifton, 2011); and (5) many women who are sexually responsive to their partners do not achieve orgasm through coitus (Laan et al., 2013).

Psychological Interventions

Recent reviews of the efficacy of psychosocial interventions for the treatment of female orgasmic disorders have concluded that CBT including directed masturbation is effective in helping women to become orgasmic (Heiman, 2002; Laan et al., 2013; Meston, 2006; Meston et al., 2004; Rellini & Clifton, 2011). Eight separate studies found that cognitive-behavioral interventions including directed masturbation were superior to a waitlist control or alternative therapy in increasing orgasmic response (Bogat et al., 1983; Delehanty, 1982; Dodge et al., 1982; Heiman & LoPiccolo, 1983; Heinrich, 1976; McMullen & Rosen, 1979, Munjack et al., 1976; Riley & Riley, 1978). Andersen (1981) did not report significant differences in orgasmic attainment between women receiving systematic desensitization therapy, directed masturbation, or a waitlist control group, although more women in the directed masturbation group became orgasmic. Follow-up at 2 months indicated that the benefits were sustained for most women. The prognosis for success in treatment for female orgasmic disorder appears more positive for women with lifelong orgasmic dysfunction than for women who acquire the dysfunction after a period of normal function. Whatever the success in achieving orgasm via masturbatory training, it begins to diminish as the woman moves from self-induced orgasm to partner-induced orgasm through manual or oral stimulation or intercourse-induced orgasm without manual stimulation. For example, one study reported that 100% of women were able to become orgasmic through masturbation, whereas only 47% of these women reported orgasm during coitus (Heinrich,

1976). Successful outcomes have been reported using a variety of treatment formats, including individual, conjoint, and group therapy and bibliotherapy. It is notable that most of these studies were performed several decades ago.

Results from other approaches including systematic desensitization were mixed. Two studies reported that "coital realignment" therapy was superior to a control group treatment (Eichel et al., 1988; Hurlbert & Apt, 1995). Coital realignment therapy involves instructing the male to position himself up and forward on his female partner to increase clitoral stimulation (Eichel et al., 1988).

Pharmacotherapy

No agent has been approved for the treatment of female orgasmic disorder in the United States; as a result, there have been few controlled trials of agents to treat female orgasmic difficulties (Ishak et al., 2010). In trials for other indications, there is evidence that certain agents facilitate orgasm, particularly in postmenopausal women. To this end, trials of testosterone therapy in postmenopausal women have found that testosterone supplementation improves various aspects of sexual function, including orgasm (Braunstein et al., 2005; Davis et al., 1995, 2006, 2008; Nathorst-Boos et al., 2006; Shifren et al., 2000). Controlled trials have also indicated that tibilone, a drug with estrogenic, progestogenic, and androgenic properties, has been found to improve measures of orgasmic capacity (Uygur et al., 2005).

Other compounds have been found to improve orgasmic function in women in controlled studies of populations selected for other indications. For example, bupropion was found to increase orgasm completion in women with HSDD (Segraves et al., 2004), and sildenafil was found to increase orgasmic response in a group of women with normal libido who came for treatment of arousal problems (Caruso et al., 2001). Other investigators have not reported benefit using sildenafil in women complaining of problems with desire and arousal (Basson & Brotto, 2003). Randomized placebo-controlled trials have indicated statistically significant benefits on various aspects of sexual function but not orgasm function from a dietary supplement marketed as ArginMax (Ito et al., 2006) and a topical botanical produce marketed as Zestra (Ferguson et al., 2010). One study did not find an effect of gingko biloba on ability to achieve orgasm (Meston et al., 2008).

Genito-Pelvic Pain/Penetration Disorder

As discussed earlier, GPPD is a new *DSM-5* diagnosis that combines elements of vaginismus and dyspareunia (Binik, 2010a, 2010b). The current cognitive-behavioral model for understanding dyspareunia is a circular one, which assumes that catastrophic memories of pain during intercourse lead to fear of pain and hypervigilance, which in turn contribute to pelvic floor muscle tone and increased pain (Ter Kuile et al., 2010). Similarly, fear of pain during vaginal penetration could provoke hypervigilance and avoidance of sexual activity (Borg et al., 2012). Given this model, one would assume that personality features of anxiety-proneness and somatization as well as certain relationship factors could be involved in the maintenance of vaginismus and sexual pain disorders. Studies have found catastrophic pain cognitions to be common in women with vaginismus (Borg et al., 2012) and indeed many treatment centers employ a multidisciplinary approach, including mental health professionals, in the treatment of pelvic pain penetration disorders (Reissing, 2012). However, it is impossible to ascertain whether the psychosocial issues identified are the result of the problem or whether they play a significant role in the genesis or maintenance of the difficulties. Since the literature before 2013 was separately reported for dyspareunia and vaginismus, this review will follow that convention.

Vaginismus can be classified as lifelong (primary) or acquired (secondary). Lifelong vaginismus is sometimes referred to as "unconsummated marriage." The usual treatment is the use of graduated vaginal dilators, a technique introduced by Sims in 1861. There is a long history of the use of graduated dilators for this condition, and many clinicians use a cognitive-behavioral approach including the gradual progression of vaginal dilators of progressively larger diameters (in vivo desensitization) as the preferred intervention. Numerous case histories and clinical series report this to be a highly effective intervention, with success rates ranging from 70% to 100% (Crowley et al., 2009). Several recent review articles have concluded that current evidence of less-than-optimal quality suggests that this approach is effective (Crowley et al., 2009; McGuire & Hawton,

2001). There are only five studies that meet minimal criteria to be reviewed as controlled studies of the psychological treatment of vaginismus (Al-Sughayir, 2005; Jarrousse & Poudat, 1986; Schnyder et al 1998; Ter Kuile et al., 2007; van Lankveld et al., 2006). Of these studies, only one used a randomized allocation to treatment or to a waitlist control group (van Lankveld et al., 2006). In this study, cognitive-behavioral group psychotherapy and bibliotherapy were both found to be superior to a waitlist control group. The 10-session, 2-hour group therapy led by a mixed-sex co-therapy team was not superior to minimum-contact bibliotherapy. Bibliotherapy consisted of a 50-page manual on the treatment of vaginismus plus a CD-ROM detailing relaxation and sexual fantasy exercises. Only 9% of the patients receiving group psychotherapy reported successful vaginal penetration at the conclusion of therapy as compared to 14% in the bibliotherapy group. This success rate was dramatically lower than those previously reported in the literature. The lack of controlled studies validating the efficacy of in vitro desensitization should not be interpreted as indicating that this type of therapy is ineffective; there have been only a handful of controlled studies of the efficacy of this treatment, in contrast to large numbers of uncontrolled trials finding this intervention to be effective. Remission rates of vaginismus without intervention appear to be quite low (Crowley et al., 2009). Although hypertonus of the pelvic floor is a possible component of the pain involved in vaginismus, there is no evidence that physical therapy of the pelvic floor is a necessary component of the treatment for vaginismus (Rosenbaum, 2007). There is, however, some evidence to suggest that botulinum neurotoxin injection into the bulbospongiosum muscle is helpful for some women with vaginismus (Pacik, 2011).

The literature concerning the treatment of dyspareunia is difficult to evaluate for multiple reasons, including (1) the high placebo response rate noted; (2) the relatively high rate of remission of symptoms without intervention; (3) uncertainty regarding whether associated psychosocial variables are simply the consequence of the disorder rather than being of etiological significance; (4) conditions of varying etiologies being similarly labeled; and (5) varying use of terminology. In *DSM-IV-TR*, dyspareunia was subtyped as lifelong or acquired, but in clinical practice, the subtype of deep or superficial is more commonly employed. Deep dyspareunia is considered almost always to be organic in etiology and often a symptom of endometriosis (Steege & Zolnoun, 2009). Most of the research concerning psychosocial correlates of dyspareunia concerns superficial dyspareunia (pain in the vaginal vestibule). Various terms have been employed to describe superficial dyspareunia: vulvodynia, vulvar vestibulitis, provoked vestibulitis, and provoked vulvodynia (Boyer et al., 2011; Fugl-Meyer et al., 2013). Although pain can be generalized and occur in multiple contexts, the most common clinical presentation is pain provoked by coitus or attempted vaginal penetration.

In many cases, the pain described seems out of proportion to any pathology identified; in many cases no clear organic etiology can be identified. This has led to the hypothesis that repetitive mild tissue injury may lead to neurogenic inflammation and lowered pain thresholds. Spasm of the pelvic floor musculature (guarding) frequently accompanies provoked vulvodynia and may contribute to the pain experienced (Rosenbaum, 2007). Some have also hypothesized that chronic subthreshold negative stimuli may also lead to central sensitization to pain stimuli. A variety of psychological variables have been reported to be associated with provoked vulvodynia, including negative attitudes toward sexuality, depression, anxiety, sexual abuse, and insecure attachment styles (Granot et al., 2011; Landry & Bergeron, 2011). In the absence of prospective studies, one cannot ascertain whether the psychological factors are the results of pain or whether they play a significant etiological role.

Evaluation of studies of efficacy of various treatment interventions should take into consideration that spontaneous remission rates of 30% (Steege & Zolnoun, 2009) and placebo-response rates of 50% have been reported (Petersen et al., 2009). Thus, the outcomes of any study that did not employ a placebo or no-treatment condition have to be regarded with skepticism. Although many centers use a biopsychosocial model of intervention (Sadownik et al., 2012; Spoelstra et al., 2011), the evidence supporting the efficacy of this approach is limited. Schultz and colleagues (1996) did not find behavior therapy plus surgery to be superior to behavior therapy alone in a study of 14 women. Bergeron and colleagues (2001, 2008) studied the relative efficacy of CBT, electromyographic feedback, and vestibulectomy in women with provoked vestibulodynia. All interventions demonstrated apparent efficacy, although the surgical intervention was statistically superior to the other interventions. None of the studies mentioned above

employed a no-treatment condition. Accordingly, one has to conclude that there is minimal evidence to date supporting cognitive-behavioral interventions for dyspareunia.

There have been reports of high success rates using surgical interventions. However, there is a paucity of randomized trials evaluating surgical approaches (Tommola et al., 2010). Randomized double-blind trials support the use of vaginal estrogens (Krychman, 2011) and intravaginal dehydroepiandrosterone (Labrie et al., 2011) to treat dyspareunia in postmenopausal women. Although botulinum toxin has been described to be effective in the treatment of dyspareunia, a double-blind study comparing botulinum injection to saline injection found no difference in outcomes between the two approaches (Petersen et al., 2009).

Substance-Induced Sexual Dysfunction

The diagnostic entity of substance-induced sexual disorders (i.e., sexual disorders associated with drug intoxication and with the use of prescribed medication) was introduced in *DSM-IV*. The name was modified in *DSM-5* to substance/medication-induced sexual dysfunction. A variety of chemical agents have been associated with sexual dysfunction. Most of the reports concern substances of abuse, antihypertensive agents, and psychiatric drugs (Segraves & Balon, 2004).

Sexual dysfunction has long been suspected to be related to chronic alcohol abuse. In particular, it has been assumed that chronic alcohol abuse in males is associated with ED (Miller & Gold, 1988; Palha & Esteves, 2008; Schiavi, 1990). Although less evidence is available concerning the effects of chronic alcohol abuse in females, it appears that chronic alcohol abuse may also be detrimental to female sexual function (Amidu et al., 2010; Rosen, 1991; Segraves, 2010b; Smith et al., 2012). There is considerable evidence that chronic alcohol abuse has deleterious effects on hypothalamic-pituitary and testicular function (Schiavi, Stimmel, Mandeli, & White, 1995). Chronic alcohol abuse is also associated with damage to the central nervous system, as manifested by dementia and Wernicke-Korsakoff syndrome. Peripheral polyneuropathy associated with myelin and axon degeneration is a common neurological complication of chronic alcoholism. Thus, there are several mechanisms by which chronic alcohol abuse could cause sexual dysfunction.

There is abundant evidence documenting the deleterious effects of nicotine on male erectile function (Palha & Esteves, 2008). The impact is related both to the average number of cigarettes smoked and number of years as a smoker. Smoking has a deleterious effect on the vascular component of penile erection. It is less clear that nicotine has a harmful effect on female sexuality.

Cannabis use is perceived by many users to have a beneficial effect on the experience of sexual pleasure, the ability to relax with a sexual partner, and the experience of sexual fantasies. However, there is some evidence that cannabis use may be associated with difficulty achieving orgasm in women (Christensen et al., 2011; Johnson et al., 2004).

Evidence concerning the effects of opioids on sexual function has been uniform and convincing. The evidence consists of anecdotal reports, surveys, and clinical studies. All the studies are consistent in finding diminished libido while the person is on narcotics (Abel, 1985). Methadone has also been found to be associated with male sexual dysfunction (Brown et al., 2005). Retrospective studies suggest that normal libido returns during drug-free periods (Segraves, Madsen, Carver, & Davis, 1985).

Cocaine and amphetamine use has been reported to cause increased libido and spontaneous erections (Abel, 1985). However, there is evidence that chronic abuse of these agents may lead to decreased libido and other sexual dysfunctions (Palha & Esteves, 2008; Siegel, 1982). It is unclear whether sexuality returns to baseline during abstinence from these agents.

Most of the antihypertensive drugs have been reported to cause erectile problems (Rosen & Leiblum, 1995; Segraves, 1988, 2010; Segraves et al., 1985). Case reports also suggest that many other agents, including antiarrhythmic agents, digoxin, and hypolipidemic agents, may be associated with erectile problems. Unfortunately, most of these reports do not include control groups or use appropriate measures of sexual function. Sildenafil appears capable of reversing erectile problems in patients with hypertensive arterial disease.

Psychiatric drugs have also been reported to cause sexual problems. This is true of almost all classes of psychiatric drugs (Segraves, 2003, 2010). Most of the evidence concerning the action of these drugs comes

from clinical reports. Most of the controlled studies are of antidepressant drugs. Benzodiazepines have been frequently reported to cause delay in orgasm. This has been reported with chlordiazepoxide, lorazepam, diazepam, and alprazolam (Segraves, 1995a, 1995b). A double-blind controlled study by Riley and Riley (1988) demonstrated a dose–response relationship between diazepam dose and orgasmic delay.

Most of the aliphatic, piperidine, and piperazine phenothizines have been reported to cause ejaculatory and erectile problems (Labbate, 2008; Segraves, 2010a). The few studies of sexual function in female patients treated with antipsychotics indicate that anorgasmia may be an unwanted side effect. Antipsychotic-induced sexual dysfunction has been reported to correlate with prolactin elevation. There has been interest in whether the newer prolactin-sparing antipsychotics would have a lower incidence of sexual dysfunction. At this point, the evidence is inconclusive, partly because of the high prevalence of sexual problems in patients with untreated schizophrenia (Aizenberg et al., 1995; Montejo et al., 1998) and partly because of methodological problems in assessment. Most reports are in agreement that risperidone causes more sexual dysfunction than olanzapine (Tran et al., 1997) and that the sexual problems with risperidone appear dose-related (Marder & Meibach, 1994). Aripiprazole also appears to have a low incidence of sexual dysfunction (Serretti & Chiesa, 2011). There have been case reports of antipsychotic-induced sexual dysfunction being reversed by sildenafil (Salerian et al., 2000; Segraves, 1999). There have been unconfirmed case reports of amantadine, bromocriptine, and cabergoline being used to reverse antipsychotic-induced sexual dysfunction.

Most of the antidepressants available in the United States have been reported to cause sexual dysfunction, with the possible exceptions of bupropion, mirtazapine, and nefazodone (Clayton & Balon, 2009; Segraves, 1995a, 1995b). This phenomenon has been confirmed in double-blind studies of many of the antidepressants (Feiger, Kiev, Shrivastava, Wisselink, & Wilcox, 1996; Harrison et al., 1985; Kowalski, Stanley, & Dennerstein, 1985; Monteiro, Noshivani, Marks, & Lelliott, 1987; Segraves, 2010a; Segraves et al., 2000). The most commonly reported sexual side effects are anorgasmia and ejaculatory delay. The incidence of sexual problems appears to be relatively similar among the SSRIs and dual reuptake inhibitors except that vilazodone and duloxetine appear to have a lower incidence of associated sexual dysfunction (Clayton & Balon, 2009). Paroxetine appears to have a higher incidence of anorgasmia than the other selective reuptake inhibitors. A variety of interventions have been suggested for antidepressant-induced sexual dysfunction. These include drug holidays, changing time of dose, lowering dose, waiting for tolerance to develop, and the use of antidotes. Numerous antidotes have been reported in case reports. These include the addition of bupropion, mirtazapine, nefazodone, yohimbine, cyprohepatadine, amphetamine, and many others (Rosen et al., 1999). The only antidotes proven effective in double-blind trials are sildenafil (Hargreave, 1998) and buspirone (Landen et al., 1999) in male sexual dysfunction and sildenafil for serotonergic antidepressant-induced anorgasmia in women (Nurnberg et al., 2008).

FUTURE DEVELOPMENTS

The past decade has witnessed extensive research on the pharmacological treatment of human sexual disorders, especially erectile disorders. Following the successful launch of the PDE5 inhibitors, there has been a search for compounds that facilitate sexual responsiveness in women. Because low sexual desire is the most common complaint in female patients, pharmacological research has focused on compounds that target the central nervous system. This research will contribute to our understanding of the neurophysiological substrate for human sexuality. Psychosocial variables appear to be more salient in female than in male sexual response. A search for effective interventions for female sexual dysfunction will undoubtedly increasingly use the biopsychosocial model. As we gain a better understanding of the relative contributions of biological and psychological influences on human sexuality, this will facilitate the development and deployment of targeted interventions.

There is a need for more controlled studies of the efficacy of psychological therapies for the sexual dysfunctions. The evidence for the efficacy of psychological therapies is weaker than that for pharmacological interventions, so we have minimal information regarding which components of CBT are essential or when this therapy is indicated. CBT for sexual dysfunctions is still in its formative stage. In the next

decade, one would expect detailed study and identification of its effective components. Similarly, one would expect the development of different models of psychotherapy for sexual problems that are predominantly psychogenic in contrast to models of therapy for problems that are predominantly biogenic.

In summary, the past decade has been an exciting time for professionals involved in the treatment of sexual dysfunctions, and the next decade has the promise to be even more engaging.

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23

Psychosocial Treatments for Substance Use Disorders

Daniel M. Blonigen
John W. Finney
Paula L. Wilbourne
Rudolf H. Moos

Based on the findings of meta-analyses, as well as type 1 and type 2 randomized controlled trials (RCTs), the most effective psychosocial modalities for treating substance use disorders (SUDs) are cognitive-behavioral interventions, motivational interviewing (MI) and motivational enhancement therapy (MET), contingency management (CM), community reinforcement approach (CRA), behavioral couples and family therapies, and 12-Step facilitation (TSF). The foci of these interventions include substance use behavior, as well as patients' life contexts and social and personal resources. Limited evidence is available for these interventions' differential effectiveness, suggesting that they operate through common mechanisms of change. Brief interventions are highly effective in the treatment of alcohol use disorders. However, as stand-alone treatments, they are best suited for individuals with mild to moderate alcohol use problems. Regardless of modality, therapists who are interpersonally skilled, empathic, and nonconfrontational, and who develop a strong therapeutic alliance, are more effective at helping patients achieve better outcomes. Residential care should be reserved for patients with greater substance use severity, limited social resources, and/or significant psychiatric and medical comorbidities. However, an individualized approach marked by variable intensity of continuing care and ongoing monitoring is needed to address the high rate of relapse in this population. A challenge for the field is to determine how to best implement empirically supported interventions in real-world clinical settings so that they are cost-effective; reach the patient populations in most need of the intervention; produce positive outcomes; and are adopted by clinical providers, delivered as intended, and integrated into routine practice.

INTRODUCTION

SUDs are a serious global public-health problem (Rehm et al., 2009). For example, illicit drug dependence directly accounted for 20 million disability-adjusted life years lost worldwide in 2010 (Degenhardt et al., 2013). Combined with extensive indirect costs such as premature mortality, lost productivity, crime, and increased health care utilization, SUDs also impose a significant economic burden (Wickizer, 2013). For example, in 2006 the economic costs of excessive drinking in the United States were estimated to be over $223 billion (Bouchery et al., 2011). These estimates are on par with the costs of

other major health-risk behaviors, such as smoking, and have prompted the Robert Wood Johnson Foundation (2001) to declare SUDs the "number one health problem in the U.S."

Much of this toll derives from substance use that falls short of meeting diagnostic criteria for an SUD (Rossow & Romelsjö, 2006). However, even among individuals who have an SUD, the majority recover on their own without treatment (Dawson et al., 2006). Nevertheless, a sizeable portion of the total population of individuals with SUDs turns to treatment after their own attempts at change have failed. Among those with an alcohol use disorder or illicit drug use disorder in the United States in 2012, approximately 8% and 15%, respectively, sought treatment in the past year (Substance Abuse and Mental Health Services Administration, 2013), and individuals who have both a drug use disorder and a comorbid psychiatric disorder are more likely to seek treatment (Compton et al., 2007). These figures highlight the importance of research to identify treatments for SUDs that are efficacious (i.e., yield positive effects under controlled research conditions) as well as effective when delivered routinely in real-world clinical settings.

We review psychosocial interventions with the most empirical support for treating SUDs in this chapter. Pharmacological treatments, combined with or independent of psychosocial approaches, and comparative effectiveness studies of psychosocial versus pharmacological approaches are covered elsewhere in this volume. We also consider promising new psychosocial treatments with accompanying data on their efficacy and/or effectiveness in the chapter. Overall, our emphasis is on research reported since publication of the last version of this chapter in 2007. Next, we review recent evidence on potential mechanisms of change for these psychosocial treatments. Following that, we update research on (a) the role of therapist characteristics and the therapeutic alliance in treatment outcomes; (b) the linkages between the duration and amount of treatment and outcome; (c) the settings and formats in which treatments are delivered; and (d) evidence for the impact on outcome of matching patients to specific SUD treatments. We conclude the chapter by commenting on the limits of our ability to identify evidence-based treatments and summarize "what works" in the treatment of SUDs. In reporting findings from specific studies, we use the standards of Cohen (1988) to interpret the magnitude of effect sizes (i.e., small = ~0.2, medium = ~0.5, and large = ~0.8). For a more practical interpretation, however, the reader is referred to the binomial effect size display (Rosenthal & Rubin, 1982), which translates effect sizes into the "success rate" of a treatment or procedure. Based on this approach, the above-noted small, medium, and large effect sizes would translate into success rates (e.g., abstinence or significant reductions in drinking at the end of treatment or at some follow-up time point) of approximately 55%, 62%, and 69%, respectively, among participants in the treatment condition, relative to a 50% rate in a comparison group (Miller & Manuel, 2008; Randolph & Edmondson, 2005).

Treatments may be more or less effective for individuals with differing levels of substance use severity. Thus, an important consideration is the changes made to the classification of SUDs in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*-5; American Psychiatric Association [APA], 2013; see also Hasin et al., 2013). Most notably, a single diagnosis of "substance use disorder" is now listed, which combines symptoms that were previously separated between diagnoses of substance abuse and substance dependence. The former symptom of recurrent substance-related legal problems has been deleted; a new symptom, craving for one or more substances, has been added. A diagnosis of SUD can be applied to nine classes of substances (alcohol; cannabis; phencyclidine; other hallucinogens; inhalants; opioids; sedatives, hypnotics, and anxiolytics; stimulants; tobacco) and is met if 2 or more out of 11 symptoms (covering domains of impaired control, social impairment, risk use, and pharmacological criteria) are observed within a 12-month period. For classes of drugs for which there is a lack of evidence for withdrawal symptoms (i.e., phencyclidine, other hallucinogens, and inhalants), a maximum of 10 symptoms is listed. Further, new indicators for severity (mild = presence of two or three symptoms; moderate = presence of four or five symptoms; severe = presence of six or more symptoms) are specified. Based on our review, essentially all prior studies that diagnosed patients likely identified individuals who would still be diagnosed with an SUD using the new *DSM*-5 criteria. Accordingly, the overall conclusions of the literature to be reviewed likely hold for individuals diagnosed as having SUDs via *DSM*-5. As a possible exception, most studies of brief interventions have focused primarily or wholly on individuals with alcohol use "problems" of mild to moderate

severity, which may or may not meet criteria for a diagnosis in either the prior or current nomenclature.

EFFICACY/EFFECTIVENESS OF COMMON PSYCHOSOCIAL TREATMENT MODALITIES

Summarizing the empirical literature on the effectiveness of psychosocial treatment modalities for SUDs presents numerous challenges. For example, most of the relevant research has focused separately on treatment of alcohol and drug use disorders, despite the substantial overlap between these disorders among individuals in the general population (Stinson et al., 2005) as well as among those who seek treatment (Hartzler et al., 2011). Further, systematic comparisons of the effectiveness of psychosocial treatment modalities are hampered by variations across relevant studies on a range of key dimensions (e.g., characteristics of the sample, the efficacy/effectiveness of the comparison group, number of outcomes tested; time interval in which outcomes were compared; statistical power; Finney, 2000).

"Box-Score" Reviews of Psychosocial Treatments for Alcohol Use Disorders

Four quantitative syntheses have compared the effectiveness of common psychosocial treatment modalities for alcohol use disorders (Finney & Monahan, 1996; Holder et al., 1991; Miller et al., 1998, 2003). These box-score reviews entail various approaches to aggregating evidence regarding the efficacy or effectiveness of a given modality across studies of randomized (or in some cases well-matched) controlled trials. These reviews represent the only comprehensive quantitative syntheses of the comparative effectiveness of common psychosocial treatment modalities for SUDs but are dated—for instance, the most recent review by Miller and colleagues (2003) covers controlled clinical trials published only up to 2000. Consequently, the findings of these reviews serve as a starting point and require integration with more recent studies.

Holder and colleagues (1991) derived an evidence index based on the ratio of positive (i.e., a significant and favorable treatment effect on one or more outcome variables) and negative trials of common psychosocial treatment modalities for alcohol use disorders. This approach was criticized for not taking into account variability in either the methodological quality of trials or the strength of the competition to which various treatment modalities had been compared (Howard, 1993). Accordingly, Finney and Monahan (1996) adjusted the evidence index of treatment effectiveness by taking into account factors that would make it more or less likely for a study to detect a significant treatment effect (e.g., sample size, number of comparisons conducted; whether continuous or categorical outcomes were examined) as well as information on the strength of the competition against which a given modality had been pitted.

More recent reviews by Miller and colleagues (1998, 2003) went further in addressing these issues by developing sophisticated coding systems to rate studies based on the methodological quality (e.g., the method of allocating participants to groups; rate of attrition). Miller and colleagues (2003) identified a total of 381 controlled clinical trials published through 2000. They calculated a "cumulative evidence score" that ranked specific treatment modalities for alcohol use disorders.

Table 23.1 provides the rankings of 15 psychosocial treatment modalities for alcohol use disorders with three or more controlled trials that were included in each of the four box-score reviews described above. Theoretically related modalities are grouped together and the groups are ordered based on their average rankings across the reviews. Several treatment modalities were consistently highly ranked. For example, even though the study by Holder and colleagues (1991) was criticized for not accounting for methodological quality across studies, the modalities identified as having "good evidence of effect" (i.e., brief motivational counseling, social skills training; stress management training; behavioral self-control training [BSCT]; community reinforcement approach; behavioral marital therapy) were fairly consistent with many of the highly ranked modalities from the other reviews. In addition, Martin and Rehm (2012) recently summarized all systematic reviews of the effectiveness of psychosocial treatment modalities for alcohol problems in adults that have been published since 2000 and observed that the modalities with the strongest empirical support are MET, other brief interventions, and various cognitive-behavioral interventions. These conclusions are generally consistent with the rankings of the box-score reviews, which were based on studies published prior to 2000. Notably, Martin and Rehm (2012) also concluded that, when the modalities with

TABLE 23.1 Rankings by Effectiveness Indices of 15 Psychosocial Treatment Modalities Having Three or More Studies in Holder et al. (1991), Finney and Monahan (1996), Miller et al. (1998), and Miller et al. (2003)

Modality	*Holder et al. (1991)*	*Finney & Monahan (1996)*	*Miller et al. (1998)*	*Miller et al. (2003)*
Motivational				
Brief motivational counseling	3	7	1	1
Cognitive and behavioral				
Social skills training	1	2	2	4
Stress management training	5	5	11	10
Behavioral self-control training	2	10	6	3
Cognitive therapy	9.5	11	7	6
Reinforcement				
Community reinforcement	5.5	1	3	2
Marital and family				
Marital therapy, behavioral	4	3	5	5
Marital therapy, other	8	4	10	11
Aversive conditioning				
Aversion, nausea	12	6	4	8
Aversion, covert sensitization	7	8.5	8	7
Aversion, electric shock	11	8.5	9	9
Other				
Hypnosis	9.5	15	12	12
Confrontational interventions	13	13	12	13
Education (tapes/lectures/films)	14	12	15	15
General counseling	15	14	14	14

Theoretically related modalities are grouped together and the groups are ordered based on consideration of their average rankings across the four reviews. Brief interventions and motivational enhancement therapy (MET) were separated as modalities in Miller et al. (2003), with brief interventions ranking first in effectiveness among the treatment modalities that were reviewed and MET ranking second. The average of these two rankings (1.5) was the highest ranking among the 15 modalities that were included in all four reviews.

the strongest evidence have been compared to one another in well-designed clinical trials, their effectiveness is comparable.

Systematic Reviews of Psychosocial Treatments for Illicit Drug Use Disorders

We are aware of only two systematic reviews of psychosocial interventions for the treatment of illicit drug use disorders (Dutra et al., 2008; Klimas et al., 2013). Dutra and colleagues (2008) examined the effect sizes from 34 "well-controlled" clinical trials for the treatment of cannabis, cocaine, opiates, and polysubstance use, which represented the treatment of 2,340 patients. The psychosocial interventions evaluated included CM, relapse prevention, cognitive-behavioral therapy (CBT), and treatments that combined CBT and CM. The strongest effect sizes were found for CM interventions, either in

combination with CBT (1.02) or alone (0.58), followed by relapse prevention (0.32) and CBT alone (0.28). However, the effect sizes for the specific treatment modalities were not significantly different from one another.

Given the relative dearth of research on the outcome of treatment for illicit drug use disorders, the findings by Dutra and colleagues (2008) are informative; however, there are a number of limitations to this review. Most notably, there was substantial variability in the control conditions to which the target psychosocial interventions were compared. Lacking a somewhat standard control condition makes it difficult to judge the relative efficacy of the target treatment types. Further, two empirically supported psychosocial treatment modalities—MET and TSF—were used only as control conditions and no effect sizes were reported that compared these interventions to any of the target conditions. Klimas and colleagues (2013) conducted a systematic review of psychosocial interventions to reduce drinking among individuals with concurrent problems with alcohol and illicit drug use. However, this review was limited by the paucity of the data (only four studies were identified) as well as the lack of methodological rigor of the studies.

Overviews of Effective Psychosocial Treatment Modalities

Their limitations aside, these reviews suggest that the modalities with the most support for the treatment of SUDs are motivational interventions (e.g., MET; brief motivational counseling), cognitive-behavioral interventions (e.g., social skills training; self-control training), CM, the community reinforcement approach (CRA), and behaviorally oriented couples and family therapy. Notably, these modalities have been most consistently recommended for the treatment of SUDs by a number of organizations including (but not limited to) the American Psychological Association (2013), the U.S. National Institute on Drug Abuse (NIDA, 2012), and the U.S. Department of Veterans Affairs/Department of Defense (VA/DoD) clinical practice guidelines (2009). In addition, randomized trials now provide support for TSF, which combines social environment changes with cognitive and behavioral elements. Finally, brief interventions, which are distinct from brief motivational counseling and MET, were found to have the highest effectiveness score among alcohol treatment modalities with three or more studies (Miller et al., 2003).

In the sections to follow, we review each of these treatment modalities and highlight the findings of meta-analyses when available or, in lieu of meta-analyses, the most recent type 1 (e.g., random assignment to treatment conditions; adequate statistical power) and type 2 randomized controlled studies (i.e., those that did not include one or more criteria of a type 1 study but were deemed to be of adequate methodological quality overall). We highlight studies that provide new process or outcome data on these modalities.

Cognitive-Behavioral Treatments

Broadly, CBT includes a number of interventions that target intrapersonal and interpersonal triggers for relapse via functional analysis of substance use, provide coping skills and alcohol and/or drug-refusal skills training, and increase non-use-related activities. For the sake of consistency with other reviews (Magill & Ray, 2009; Martin & Rehm, 2012), we use the term "cognitive-behavioral" to describe treatment modalities that use any of these strategies. However, it should be noted that interventions with a more cognitive focus (e.g., relapse prevention) have less support than interventions that are more behavioral or skills-focused (Miller et al., 2003).

As Table 23.1 suggests, the most highly ranked cognitive-behavioral intervention is social skills training. In this approach, patients learn how to initiate social interactions, express their thoughts and feelings more effectively, and cope with high-risk social situations and interpersonal difficulties (e.g., how to respond appropriately to criticism from others or refuse offers of drugs or alcohol). Treatment is typically in a group format to facilitate role-playing, social modeling, and receipt of feedback and is effective as either a stand-alone treatment (Eriksen, Bjornstad, & Gotestam, 1986; Monti, Gulliver, & Myers, 1994) or when combined with coping skills training (Monti et al., 1997; Monti & O'Leary, 1999).

We did not find any meta-analyses on the efficacy of social skills training per se for the treatment of SUDs; however, we did identify two meta-analyses of randomized trials of CBT for SUDs. Walters (2000) reviewed 17 trials of BSCT published between 1984 and 1997. BSCT (or "behavioral self-management training")

teaches patients social and coping skills but focuses on moderation rather than abstinence and teaches patients to set limits to drinking and self-monitor drinking habits. Walters (2000) detected a moderate effect size (0.33) across studies on measures of alcohol consumption and drinking-related problems. These effects were superior to no-treatment controls and other non-abstinence-oriented interventions. Effects were larger for BSCT relative to abstinence-oriented interventions, although not significantly so, perhaps due to the small number of trials comparing BSCT with an abstinence-oriented intervention (n = 6). In the other meta-analysis, Magill and Ray (2009) reviewed 53 RCTs of CBT (i.e., cognitive-behavioral, relapse prevention, or coping skills training) among adults diagnosed with either an alcohol use disorder or an illicit drug use disorder (total N = 9,308). A small, albeit significant, effect was observed across diverse comparison conditions, including active control comparisons (0.15). However, CBT had a large effect size (0.80) relative to no-treatment control conditions. Across studies, effects were reduced at 6 and 9 months and markedly diminished at 12 months after treatment. It is worth noting that, in this review, more cognitively oriented interventions (e.g., relapse prevention) were combined with skills-focused interventions, despite the fact that the latter have shown more empirical support (Miller et al., 2003).

Motivational Interviewing/Motivational Enhancement Therapy

Brief interventions drawing on the principles of MI (Miller & Rollnick, 2002) have strong empirical support as a treatment for SUDs, particularly alcohol use disorders. However, not all brief interventions are based on MI principles. Specifically, non-MI-based brief interventions commonly used in medical settings were regarded as a distinct treatment modality in the most recent box-score review (Miller et al., 2003). Accordingly, we review the evidence-base for "brief interventions" in a subsequent section.

MI seeks to evoke and reinforce the client's motivation for change. MI uses a client-centered approach and assumes that clients have the personal resources to change. However, it is also a directive intervention that assumes that assistance from a therapist in the context of an egalitarian relationship with the client will maximize the chances of positive behavior change, whereas a confrontational approach will impede such change. Key elements of MI include (a) empathy, (b) acceptance, (c) collaborative partnership, (d) compassion, (e) direction, and (f) evocation of client motivation. This approach can incorporate normative feedback using assessments of alcohol and other drug use to provide clients with information about the discrepancy between their level of substance use and that of most other people in the general population. MI is typically delivered in four sessions or less; however, it is defined more by the style or manner of interacting with clients than by a specific number of treatment episodes. For example, it can be used as a stand-alone intervention or as a brief intervention to increase a patient's engagement in therapy prior to the initiation of a more extended treatment modality. An important aspect of MI is its emphasis on the individual's current motivation for change in each session. Forcing discussions about ambivalence with clients who are committed to change has been shown to be counterproductive (Ashton, 2005).

Several meta-analyses have been conducted on MI (e.g., Burke, Arkowitz, & Menchola, 2003; Dunn, DeRoo, & Rivara, 2001; Rubak, Sandbaek, Lauritzen & Christensen, 2005). Rubak and colleagues (2005) found that MI had reduced the amount of alcohol consumed and the resultant blood alcohol concentration. Looking across a number of problem behaviors, they also noted that the effect of MI increased at follow-ups of 1 year or more, and that two or more sessions increased the effectiveness. Hettema, Steele, and Miller (2005) reported a significant, large effect size of MI (0.77) in the short term (i.e., 1 month or less) relative to a range of comparison conditions. This effect decreased but was still in the moderate range (0.30) at follow-up time points up to 1 year. Across all follow-up points, effects sizes were comparable for studies of alcohol (0.26) and drug (0.29) abuse. Further, treatment effect sizes were largest when MI was included at the outset of an existing treatment program, suggesting that it may be most effective as an engagement strategy or adjunct to other treatments. In another meta-analysis of MI across 18 studies (Vasilaki, Hosier, & Cox, 2006), the effect size was large (0.60) at 3 months or less; among a subset of studies (n = 9) that compared MI to an active treatment condition, the effect size was moderate (0.43).

MET is a four-session intervention based on the principles of MI and normative assessment feedback. In Project MATCH, more than 1,700 individuals

with an alcohol use disorder were randomly assigned to receive four sessions of MET, 12 sessions of CBT, or 12 sessions of TSF over a 12-week period. MET was found to be as efficacious as the other two more intensive treatments on the primary outcomes of drinks per drinking day and percent days abstinence (Project MATCH Research Group, 1997). These findings align with those from a large randomized trial of individuals with alcohol problems from the United Kingdom, which found three sessions of MET to be as effective as nine sessions of social behavior and network therapy (akin to CRA-based approaches) on drinking outcomes at a 12-month follow-up (UKATT Research Team, 2005). Regarding long-term efficacy, Adamson and Sellman (2008) reported comparable rates of heavy drinking 5 years after treatment among patients from a randomized trial who received MET or one of two control conditions (nondirective reflective listening; no further counseling); however, this finding reflected the fact that patients in the control conditions had caught up to the earlier drinking gains of the MET patients.

A few recent studies have begun to identify the effective components of MI-based interventions. Individuals with substance use problems are more likely to overestimate the amount of alcohol and drugs that other people use. The normative feedback element of MET is thought to cause a reduction in substance use by correcting the client's normative beliefs about drug and alcohol use. Using a randomized design, Martens and colleagues (2013) evaluated the efficacy of two single components of a brief, in-person MI-based intervention—personalized normative feedback and protective behavioral strategies feedback—among at-risk college-student drinkers. Relative to individuals in the protective behavioral strategies feedback condition and an alcohol education condition, those in the personalized normative feedback condition were more likely to reduce their drinking at a 6-month follow-up, and these effects were mediated statistically by changes in the clients' perceived norms about drinking at the 1-month follow-up. The benefits of personalized feedback were also supported in a meta-analysis of individual-level interventions to reduce drinking among college students (Carey et al., 2007). Thus, personalized normative feedback appears to be a key component of MET. However, most of this research has been focused on college students, so generalization beyond this population is necessarily limited.

Contingency Management

In CM-based approaches, behaviors indicating better substance use outcomes (e.g., drug-free urine screenings) are reinforced by providing patients with prizes or other incentives (e.g., vouchers with monetary value that can be exchanged for goods and services). For voucher-based reinforcement, the value of these incentives typically increases gradually with each drug-free urine analysis. The reinforcement schedules in CM are usually limited to the time in which patients are in treatment, with the majority of extant CM trials using a 12-week reinforcement schedule.

The efficacy of CM—particularly for drug use disorders and as an adjunct to other treatment programs—is supported by multiple meta-analytic reviews of randomized trials. Lussier and colleagues (2006) examined 30 randomized trials of voucher-based CM for individuals with SUDs. They concluded that CM was superior to a range of control conditions on abstinence outcomes, and that effect sizes were largest for higher-value vouchers delivered immediately after a patient met a contingency (e.g., drug-free urine analysis). Similar conclusions were reached in a meta-analytic review by Prendergast and colleagues (2006), which was not limited to trials using voucher-based reinforcement. A subsequent trial by Petry and colleagues (2007) concluded that prize- and voucher-based reinforcements (relative to standard treatment) were equally effective in achieving abstinence among outpatients who were dependent on cocaine (see also Petry & Roll, 2011). In addition, the effectiveness of CM has been demonstrated in multisite trials in the community (Petry, Alessi, & Ledgerwood, 2012), and the U.S. Department of Veterans Affairs (Hagedorn et al., 2013).

An ongoing issue in the CM literature is the efficacy of the intervention after the end of treatment. Specifically, the outcomes of most CM trials have been assessed during or at the end of the intervention (Prendergast et al., 2006), and multiple randomized trials have not found CM to maintain abstinence after reinforcements have ended (e.g., Kirby et al. 2013). However, combining CM with other effective treatment modalities such as CBT (Budney, Moore, Rocha, & Higgins, 2006; Carroll et al., 2012) or CRA (Litt et al., 2007) can lead to better long-term substance use outcomes.

Community Reinforcement Approach

CRA is a comprehensive behavioral treatment package that employs social, recreational, vocational, and familial incentives to alter the environment of individuals with SUDs. The goal is to help these individuals adopt a pleasurable and sober lifestyle that is more rewarding than, and can compete with, a lifestyle marked by alcohol and drug use (Hunt & Azrin, 1973). Basic CRA includes (a) a functional analysis to identify internal and external triggers for using substances and explore the negative and positive consequences of use; (b) a therapist–client agreement to sample time-limited periods of abstinence; (c) behavioral skills training to help clients develop problem-solving, communication, and drink-refusal skills; (d) vocational skills training; (e) social and recreational counseling to identify new sources of pleasurable activity; and (f) relapse prevention to help clients identify high-risk situations for using and how to anticipate and cope with these situations. Relationship counseling and other approaches that employ the assistance of significant family members are also incorporated in some forms of CRA (e.g., Community Reinforcement And Family Training [CRAFT]). The key emphasis of CRA-based interventions is on the development of a supportive social network and the promotion of rewarding activities that can substitute for substance use.

CRA-based interventions are among the more highly ranked psychosocial modalities for the treatment of SUDs, with their efficacy/effectiveness supported by multiple randomized trials and systematic reviews (e.g., Meyers, Roozen, & Smith, 2011; Roozen et al., 2004). Most recently, a trial of CRA found individuals randomized to a "network support" condition (vs. network support plus CM or case management) yielded 20% more days of abstinence at 27 months after treatment (Litt, Kadden, Kabela-Cormier, & Petry, 2009). Other trials, however, have not identified advantages of CRA compared to other active interventions such as MET (UKATT Research Team, 2005).

Higgins and colleagues (2003) developed a model of CRA that includes a CM component, and several trials have shown that CRA plus voucher-based CM predicts better substance use outcomes than vouchers alone for a range of substance-abusing populations (Bickel et al., 2008; Budney et al, 2006; Garcia-Rodriguez et al., 2009). Finally, CRAFT was designed to engage treatment-resistant individuals with SUDs into treatment by working through family members (e.g., showing concerned significant others how to change the home environment to reward behaviors that promote sobriety and withhold rewards when the individual uses alcohol or drugs; Meyers et al., 1998). Several randomized trials have shown that this approach improves outpatient treatment engagement among initially unmotivated drug users (Meyers et al., 2002; Miller, Meyers, & Tonigan, 1999).

Behavioral Couples and Family Therapy

Behavioral Couples Therapy and other family-based therapies involve the active participation of the spouse or partner of an individual with SUDs to effect change in his or her drinking behavior. These interventions often begin with an assessment of the patient's drinking behavior as well as the relationship between the patient and the spouse/partner. The interventions address drinking through the use of behavioral contracts and agreements, while other components assist couples in improving their relationship and resolving conflicts by enhancing communication skills, encouraging more positive exchanges and caring behaviors, and planning joint recreational activities.

Multiple randomized trials and reviews support the efficacy of these interventions to improve substance use, relationship, child psychosocial, and partner violence outcomes (McCrady, Epstein, Cook, Jensen, & Hildebrandt, 2009; Vedel, Emmelkamp, & Schippers, 2008). A trial of women with alcohol use disorders compared Behavioral Couples Therapy to individual behavioral therapy and found that the women assigned to Behavioral Couples Therapy had significantly greater improvements in percent days abstinent during treatment and at 12 months after treatment (McCrady et al., 2009). In addition, a meta-analysis of 12 randomized trials (total $n = 754$) found moderate to large effect sizes for Behavioral Couples Therapy (relative to individual-based treatments) on a range of drinking and relationship outcomes (Powers et al., 2008).

12-Step Facilitation

TSF is based on the principles of Alcoholics Anonymous (AA) and the "disease model" of addiction. This model assumes that alcohol dependence is

a chronic disease and requires a lifelong commitment to abstinence. In AA and other 12-step mutual-help groups, the goals are for participants to reduce denial over their alcohol and drug use, accept that they are powerless over the substance use, and surrender control to a "higher power." Ongoing involvement in mutual-help groups after abstinence is achieved is a central tenet of the 12-step model, and multiple studies have found greater mutual-help group attendance to be linked to a greater likelihood of long-term abstinence (e.g., Witbrodt et al., 2012). Despite these benefits, most individuals who attend mutual-help groups as part of their treatment for alcohol dependence discontinue involvement in these groups at the end of their designated treatment period (Kaskutas et al., 2005).

TSF is a highly structured and manual-based approach developed to enhance ongoing involvement in 12-step mutual-help groups. Used either as a stand-alone or adjunctive intervention, TSF involves introducing clients to the principles of the 12-step model, providing clients with information on 12-step groups in their area, and encouraging clients to set goals for 12-step meeting attendance and involvement. Although the long-term goal of this intervention is abstinence, TSF is more directly aimed at encouraging client commitment to, and participation in, 12-step groups. To this end, clients attend weekly sessions in which they are asked about their drinking habits and 12-step meeting attendance and participation and are provided with AA or Narcotics Anonymous literature applicable to the step they have reached.

The efficacy of TSF is somewhat controversial. TSF was not included in several early box-score reviews (Finney & Monahan, 1996; Holder et al., 1991) and was ranked relatively low among the treatment modalities in the Mesa Grande database (Miller & Wilbourne, 2002). For example, Miller and colleagues (2003) noted that, in five out of the six studies they identified, TSF was no more effective than comparison modalities (see also Ferri et al., 2006). However, as noted by Miller and colleagues (2003), the comparison modalities in trials of TSF have typically been well-supported treatments for SUDs (e.g., CBT); thus, TSF has faced stiffer competition than many other psychosocial treatment modalities.

In their systematic review of psychosocial treatments for alcohol problems, Martin and Rehm (2012) highlighted two large, well-designed trials that suggest that TSF is more effective than its low ranking in the Mesa Grande database suggested. First, in a large, naturalistic, multisite study of inpatients from SUD treatment programs in the U.S. Department of Veterans Affairs that were either in TSF- or CBT-oriented programs, or a mixture of the two, no differences were found among the three groups on 9 of 11 outcome variables at a 1-year follow-up (Ouimette, Finney, & Moos, 1997). Further, patients in TSF-oriented programs were significantly more likely than those in CBT-oriented programs to abstain from alcohol or drugs in the 3 months prior to the follow-up, and additional analyses suggested that this effect was mediated by patients' involvement in 12-step groups (Humphreys, Huebsch, Finney, & Moos, 1999). Second, in Project MATCH, no differences emerged among TSF, CBT, or MET groups on the primary outcomes of drinks per drinking day and percent days abstinent at 1- and 3-year follow-up assessments (Project MATCH Research Group, 1998a, 1998b). Collectively, these findings, as well as those of other randomized trials (e.g., Brown, Seraganian, Tremblay, & Annis, 2002), suggest that the efficacy of TSF may be at least as strong as cognitive-behavioral interventions in the treatment of SUDs.

As with many treatment modalities, the effectiveness of TSF is dependent on the intensity of the intervention. Timko and DeBenedetti (2007) conducted an RCT comparing intensive TSF (i.e., in addition to standard TSF, counselors actively arranged AA meeting attendance and encouraged participants to keep an AA attendance journal) versus standard TSF (i.e., participants were provided psychoeducation, given an AA schedule, and only encouraged to attend sessions). At a 12-month follow-up, patients in the intensive TSF condition reported greater 12-step meeting attendance and involvement than those in the standard TSF condition, which in turn predicted significantly lower alcohol and drug use (see also Donovan et al., 2013, regarding the efficacy of a TSF-based intervention for stimulant abusers).

Brief Interventions

Due to their practicality and efficacy, brief interventions have surged in popularity over the last decade. This is particularly true in health care settings where medical providers are often constrained by lack of time. Brief interventions range from a single 5-minute

session to three or four 30-minute sessions. Moreover, the content of brief interventions can vary considerably, from simply advising patients to reduce their drinking and drug use to norm-referenced feedback and brief lifestyle counseling (Jonas et al., 2012; Kaner et al., 2013). The FRAMES model (Miller & Sanchez, 1993) outlines six elements that are common components of empirically supported brief interventions: giving *f*eedback on the risks and consequences of substance use; emphasizing personal *r*esponsibility to change substance use; giving concrete *a*dvice on how to modify substance use; offering a *m*enu of different change options; using an *e*mpathic and nonjudgmental therapeutic style; and increasing patients' *s*elf-efficacy to change their pattern of use. These components and, accordingly, many brief interventions are guided by MI principles. However, one recent study, which analyzed data from three RCTs of brief alcohol interventions, did not find consistent evidence that the therapist's "MI spirit" was related to drinking outcomes (Bertholet, Palfai, Gaume, Daeppen, & Saitz, 2013).

Multiple reviews of type 1 and type 2 trials have concluded that brief interventions are more efficacious than no treatment for individuals with mild to moderate drinking problems, are as efficacious as more intensive interventions, and are feasible and effective in medical settings (Bien, Miller, & Tonigan, 1993; Madras et al., 2009; Miller et al., 2003; Wilk et al., 1997), particularly primary care (Kaner et al., 2013; Moyer et al., 2002). The definition of "brief" (either in terms of number of sessions or the overall length of the intervention) is not uniform across studies. However, effectiveness may be more dependent on multiple contacts than the length of individual sessions (Jonas et al., 2012). Moreover, participants assigned to brief interventions sometimes received other treatments for hazardous drinking, and most brief interventions have been compared to a no-treatment control and therefore have faced limited competition relative to more intensive treatment modalities, which are typically compared to other active treatments.

Despite these caveats, considerable evidence supports the effectiveness of brief interventions. Accordingly, more recent work has begun to consider the populations and settings best suited for these interventions, and the level or intensity needed to effect positive substance use outcomes. In terms of populations, the efficacy of brief interventions is well established with patients seen in primary care (particularly middle-aged men; O'Donnell et al., 2014) with hazardous alcohol use or mild to moderate alcohol use disorders. These interventions may be less effective with medical inpatients, patients who misuse drugs other than alcohol, or patients who are severely dependent on alcohol or other drugs (Field et al., 2010; Saitz et al., 2007; but see Srisurapanont et al., 2007).

Saitz (2010) reviewed randomized trials of alcohol screening and brief interventions for patients in primary care to determine whether those identified as alcohol dependent exhibited decreases in drinking and alcohol-related problems or increased engagement in the alcohol treatment system. Out of 16 randomized trials, 14 excluded patients with "very heavy" alcohol use or dependence, and the 2 remaining studies (Burge et al., 1997; Chang et al., 1997) offered no evidence of the efficacy of brief interventions over a no-treatment control among alcohol-dependent patients (see also Moyer et al., 2002).

Stepped-care models, which provide more intensive interventions for patients who do not respond to an initial brief intervention, may be a sensible alternative for more severely dependent individuals (Breslin et al., 1997; Sobell & Sobell, 2000). There is mixed evidence for the efficacy of a stepped-care approach for initial nonresponders (Jaehne et al., 2012). However, this may be due to a lack of sufficient power to detect group differences or a lack of differentiation between low- and high-intensity interventions in extant trials. As an exception, one randomized trial found, as hypothesized, that a stepped-care intervention was of comparable effectiveness to a full-care intervention on drinking outcomes but more cost-effective (Bischoff et al., 2008).

In terms of level of intensity, multicomponent brief interventions may be no more effective than simpler, single-component approaches. For example, Kaner and colleagues (2013) conducted an RCT of three brief interventions, each of which built on the previous ones: an informational leaflet control group; 5 minutes of structured brief advice; and 20 minutes of brief lifestyle counseling. All three groups completed the AUDIT (Saunders et al. 1993) and received norm-referenced feedback on their scores. No group differences in AUDIT scores emerged at 6- and 12-month follow-ups, suggesting that adding brief advice or lifestyle counseling did not provide incremental benefit over assessment and feedback.

Consistent with this finding, Holloway and colleagues (2007) found that providing medical inpatients with a self-help booklet was as effective as a 20-minute brief intervention in reducing their drinking. Again, however, these findings may apply primarily to individuals with more mild or moderate alcohol use problems, whereas populations marked by very heavy use or dependence may require a stepped-care approach, or more intensive interventions that include pharmacotherapy (Oslin et al., 2014).

OTHER PSYCHOSOCIAL TREATMENT MODALITIES

As shown in Table 23.1, some of the most common approaches to SUD treatment in the United States (e.g., educational tapes, lectures, books, or films; general counseling; and confrontational interventions) are among the lowest-ranked modalities. General unstructured counseling is also ineffective for the treatment of SUDs and often serves as a control condition in randomized trials. In general, confrontational approaches do not help to engage individuals in SUD treatment or improve substance use outcomes (Moyers & Miller, 2013). However, confrontation may help to engage individuals in treatment if it is delivered by an interpersonally skilled therapist in the context of an empathic and egalitarian relationship (Moyers, Miller, & Hendrickson, 2005).

Milieu therapies, such as therapeutic communities, have a longstanding tradition in the treatment of SUDs (De Leon, 2000). Generally, these approaches are based on a social learning model in which patients hold jobs and other positions of responsibility and are held accountable by their peers and by staff for fulfilling their responsibilities and adhering to program rules and norms. Although a significant positive effect for therapeutic communities relative to control conditions was reported in one meta-analysis (Prendergast et al., 2002), other systematic reviews, including the most recent box-score review (Miller et al., 2003), have either found limited or mixed evidence for effectiveness (Reif et al., 2014) or concluded that these programs were no more effective than other forms of residential treatment (Smith, Gates, & Foxcroft, 2006). In one exception, men with comorbid SUDs and other mental health disorders who were randomly assigned to a modified, 12-month therapeutic community (vs. a comparison group) had significantly greater declines in alcohol and drug use at 12 months after release from prison (Sullivan et al., 2007). The reasons for the differences across reviews are unclear but may be a function of the variability in these interventions in terms of both the target population (e.g., prisoners, seriously mentally ill patients) and setting (e.g., residential, day-treatment centers).

Other treatment modalities not included in the box-score reviews, due to either limited evidence or because they were developed after these reviews, have been gaining prominence in recent years. The Matrix Model is a multimodal treatment program, combining relapse prevention, skills training, facilitation of 12-step mutual-help group involvement, and family systems and educational approaches, to help individuals who abuse stimulants engage in treatment and achieve abstinence (Rawson et al., 1995). This model uses a nonconfrontational approach and is typically delivered in a group format on an outpatient basis, but also includes individual counseling and routine screening of drug use (Obert et al., 2000). NIDA (2012) has cited this approach as an effective treatment for SUDs; however, we are aware of only one randomized trial of this intervention. Among 978 individuals addicted to methamphetamine who were randomly assigned to treatment as usual or a 16-week manual-based form of the Matrix Model, those in the Matrix Model condition stayed in treatment longer, provided more drug-free urine samples, and had longer periods of abstinence during treatment; however, no significant differences were found between these conditions after treatment (Rawson et al., 2004).

Mindfulness-based interventions have received increasing attention over the last decade. Broadly, these interventions, which include mindfulness-based stress reduction and Acceptance and Commitment Therapy (ACT), employ behavioral exercises to help patients increase their awareness of internal and external triggers to substance use. In contrast to avoidance-based coping strategies, the goal is to focus attention on the full experience of internal and external phenomena. Systematic reviews have concluded that these interventions are more effective than control conditions in reducing substance use (Zgierska et al., 2009); however, these reviews identified very few randomized trials and highlighted methodological limitations to these trials (e.g., high dropout rates in the treatment condition).

In a recent trial of ACT, Smout and colleagues (2010) reported no significant differences on

outcomes between adults dependent on methamphetamine who were randomly assigned to ACT or CBT. However, the "competition" in this case (i.e., CBT) is itself an intervention with strong support for the treatment of SUDs. Further, Luoma, Kohlenberg, Hayes, and Fletcher (2012) conducted a randomized trial to test whether a group-based ACT intervention focused on shame improved aftercare attendance and reduced substance use among patients in a residential SUD treatment program. Intent-to-treat analyses indicated that, relative to patients assigned to treatment as usual, those in the ACT condition had greater treatment attendance and fewer days of substance use at a 4-month follow-up. Mindfulness-based interventions, particularly ACT, show promise; however, the limited number of rigorous trials and mixed findings suggest caution and encourage more research on these approaches.

The past decade has also seen a rapid increase in integrated treatments for individuals with both SUDs and other psychiatric disorders. This issue is important, given the high prevalence of comorbid mental health disorders among SUD patients and their relatively poor prognosis (Nunes & Rounsaville, 2006). However, the evidence for effectiveness is mixed, and existing studies are burdened by small samples, inconsistent definitions of comorbidity, and a wide range of populations and treatments (Hunt et al., 2013; Tiet & Mausbach, 2007). Although many of these studies have employed one or more of the empirically supported treatments described here, some interventions were designed specifically as a treatment of SUDs and another mental health condition. For example, Seeking Safety was developed for the treatment of SUDs and comorbid posttraumatic stress disorder (PTSD). However, only a handful of RCTs have been conducted. In a large multisite trial of women with comorbid SUD and PTSD who were treated with either Seeking Safety or an active comparison (a health education group), no significant group differences emerged on substance use outcomes at any of three follow-up assessments (Hien et al., 2009). By contrast, in a trial of U.S. military veterans in an outpatient SUD clinic, those randomized to Seeking Safety (vs. treatment as usual) had greater treatment attendance at the end of the intervention and better drug use outcomes (but not alcohol use or PTSD outcomes) at a 6-month follow-up (Boden et al., 2012).

Finally, due to their low cost and ease of dissemination, computer- and Web-delivered interventions have received increasing attention (Cucciare et al., 2012). These are typically brief interventions with content that is largely CBT-based (e.g., moderation training akin to BSCT; Hester et al., 2009) and/or MI-based (e.g., assessment and personalized feedback; White et al., 2010). Multiple meta-analyses of type 1 and 2 trials have demonstrated the efficacy of computer- and Web-delivered interventions, although most studies have been limited to alcohol use among college students. Across eight trials identified by White and colleagues (2010), medium-sized treatment effects for several distinct drinking outcomes were observed. In their meta-analysis of the efficacy of computer-delivered interventions to reduce drinking among college students, Carey and colleagues (2009) concluded that these interventions show a small, albeit significant, treatment effect when compared to assessment-only conditions and are roughly equivalent to other alcohol-related interventions (e.g., alcohol education). Carey and colleagues (2012) also conducted a meta-analysis to determine the relative efficacy of face-to-face versus computer-delivered interventions for college drinkers. Each mode of delivery had a significant treatment effect relative to controls at short-term follow-ups (<13 weeks); however, direct comparisons conducted in four trials favored face-to-face over computer-based interventions.

These reviews provide support for the delivery of brief interventions for alcohol misuse using Web-based approaches but also suggest some caution given the small effect sizes, the heterogeneity of outcome measures and follow-up periods, and the predominant focus on college-student populations. Further, the efficacy of this mode of delivery may be limited in comparison to face-to-face interventions. On the other hand, some individuals, particularly those in rural settings, may have very limited treatment options, in which case a no-treatment control may be an appropriate comparison condition when evaluating the efficacy of Web-based interventions.

MECHANISMS OF CHANGE UNDERLYING EFFECTIVE TREATMENT MODALITIES

The last decade has seen a marked emphasis on identifying why some psychosocial treatments for SUDs are effective (Kiluk & Carroll, 2013; Longabaugh & Magill, 2011) and others are not. Identifying the "active ingredients" of effective treatments can inform

the development of brief versions of treatments that eliminate ineffective components of more intensive protocols, inform the development of newer, more theoretically anchored treatments, and facilitate implementation of empirically supported treatments into routine care. The bulk of the research literature has been limited to secondary analyses of trial data using mediational models (MacKinnon & Fairchild, 2009).

Focusing on mechanisms of change in MI, a review by Apodaca and Longabaugh (2009) identified 19 studies of MI that provided data on at least one link in a mediational causal model. Client change talk and experience of discrepancy (i.e., discomfort with how one's current behavior diverges from one's goals and values) had positive effects on outcomes. More recently, Morgenstern and colleagues (2012) conducted a trial that experimentally manipulated the active ingredients of MI and similarly concluded that client change talk is a key mediator of the effects of MI.

With respect to CBT, Morgenstern and Longabaugh (2000) reviewed 10 randomized trials that examined possible mediators of the effects of CBT and found little empirical support for any of the proposed mechanisms. However, a more recent analysis found that quality of coping skills acquired, rather than the sheer number of skills, was a significant mediator of the effects of CBT on reduced drug use after treatment (Kiluk et al, 2010). Further, in secondary analyses of data from the COMBINE trial (i.e., combined pharmacotherapy with CBT and/or medication management to treat individuals with alcohol dependence), receipt of drink-refusal training was associated with significantly fewer days of drinking during treatment and 12 months after treatment, and these effects were mediated by changes in self-efficacy (Witkiewitz, Donovan, & Hartzler, 2012).

Relative to the aforementioned modalities, studies attempting to identify the active ingredients of CM and CRA have been limited. However, Lussier and colleagues (2006) reported that improved treatment attendance (see also Hagedorn et al., 2013) and medication compliance may account for the beneficial effects of CM on patient outcomes, and Litt, Kadden, Kabela-Cormier, and Petry (2008) suggested that increased self-efficacy may be a common mechanism of behavior change for CM and treatment modalities. In addition, higher rates of abstinence 2 years after treatment among individuals in a network support intervention (analogous to CRA) was mediated by more AA attendance and involvement and greater self-efficacy and coping skills at 15 months (Litt et al., 2009).

Regarding 12-step approaches, Kelly and colleagues (2009) identified 13 studies that conducted full mediational tests of the effects of 12-step groups. They concluded that these groups help individuals recover from substance use via enhancement of self-efficacy, coping skills, and motivation, and increasing engagement in adaptive social networks (see also Kelly et al., 2011). The above-noted findings of Litt and colleagues (2009) regarding mediators of network support may also apply here, given that this intervention was also partly based on the TSF intervention from Project MATCH.

Although these studies identified significant mediators for many of the effective psychosocial treatments for SUDs, a review of research on the mechanisms of action for MI, CBT, Behavioral Couples Therapy, and TSF provided minimal support for the belief that these treatments work via unique active ingredients (Morgenstern & McKay, 2007). Rather, it has been suggested that the effectiveness of these interventions is driven by common factors that cut across these ostensibly distinct modalities (Finney et al., 1998; Kiluk & Carroll, 2013; Lussier et al., 2006). Common processes may explain the limited evidence for specific mediators of the effects of individual treatment approaches, or for the effectiveness of one modality over others in the treatment of SUDs (Dutra et al., 2008; Martin & Rehm, 2012). A prominent example of this is the Combined Behavioral Intervention from the COMBINE trial (Anton et al., 2006), which demonstrated that MET, CBT, and TSF are not mutually exclusive. A review by Moos (2007) suggested that a select number of social processes that protect against the development of SUDs (i.e., support, goal direction and structure; availability of prosocial activities and rewards to compete with substance use; a focus on abstinence-oriented norms and models; and development of coping skills and increased self-efficacy) may also be active ingredients of effective psychosocial treatments of SUDs.

An alternative conceptualization of mechanisms of change, based on neuroscience research, focuses on the cognitive, affective, and learning processes that underlie changes in substance use among treated individuals. For example, a recent review by Stanger and colleagues (2013) highlights changes in decision

making, such as delay discounting (i.e., shifting the preference for the immediate rewards of drug use to the delayed reward of abstinence), as a key mediator of SUD treatment outcomes, particularly in CM-based approaches. Further, a study of individuals who participated in an RCT of computer-assisted CBT for SUDs, which included functional MRI and neuropsychological testing before and after treatment, suggested that changes in the neural systems involved in cognitive control, impulsivity, and attention may drive the effects of behavioral therapies for SUDs (Devito et al., 2012).

ROLE OF THERAPEUTIC ALLIANCE AND THERAPIST CHARACTERISTICS

As defined by Lebow and colleagues (2006), the therapeutic alliance reflects the collaborative relationship and emotional bond between the patient and therapist, and a shared agreement regarding the specific goals and tasks of treatment. The importance of the therapeutic alliance to SUD treatment outcomes is well established. For example, a stronger working alliance was a significant predictor of better drinking outcomes across all three treatment modalities in Project MATCH. This finding held for both therapist and patient ratings of the alliance in the outpatient arm, and for therapist ratings in the aftercare arm (Connors, Carroll, DiClemente, Longabaugh, & Donovan, 1997). Similar findings have emerged for therapist and patient ratings of alliance in a study of opioid-dependent patients in methadone treatment (Belding, Iguchi, Morral, & McLellan, 1997).

In their review of the literature on therapeutic alliance and substance use outcomes, Meier and colleagues (2005) noted that early therapeutic alliance is a consistent predictor of reduced substance use during treatment, but not of posttreatment outcomes. In this regard, a key mechanism in the alliance–outcome link may be whether an early alliance enhances patients' engagement and retention in treatment. For example, a strong therapeutic alliance early in treatment is associated with a longer length of stay in treatment among patients with a drug use disorder (Simpson, Joe, & Rowan-Szal, 1997), among couples in marital therapy for drinking problems (Raytek, McCrady, Epstein, & Hirsch, 1999), and among emergency department patients with drinking problems (Baird et al., 2007).

A key contributor to the quality of the therapeutic alliance is the interpersonal style of the therapist. Indeed, therapist characteristics have a robust impact on SUD patients' outcomes that may be greater than the impact of any particular treatment modality (Luborsky et al., 1986; Najavits & Weiss, 1994). Several studies have found dramatic variations across therapists with regard to their impact on SUD treatment retention and outcomes (Najavits et al., 2000; Najavits & Weiss, 1994). For example, Najavits and colleagues (2000) found significant therapist differences in four studies of treatment retention, which ranged from 29% to 77%; in one of these studies, the average effect size among therapists on treatment outcomes ranged from 0.13 to 0.74. Further, data from large randomized trials of SUD patients have indicated that therapist variables are primarily responsible for the association between alliance and outcomes (Baldwin, Wampold, & Imel, 2007; Crits-Christoph et al., 2009; see also Laska et al., 2013).

In general, therapist differences are not attributable to level of professional training, years of clinical experience, recovery status, or the characteristics of patients being treated (Lebow et al., 2006; Najavits & Weiss, 1994). Rather, therapists who are more interpersonally skilled and empathic and less confrontational tend to have better outcomes, and in one study these therapist characteristics were associated with greater patient self-efficacy and coping skills acquisition at the end of treatment (Ritter et al., 2002). Importantly, these therapist characteristics are also congruent with the principles of MI, and various studies have concluded that the benefits of MI are maximized by a less directive (Karno & Longabaugh, 2004) and more empathic therapeutic style (Baird et al., 2007). However, all major treatment modalities reviewed here emphasize the importance of a good working alliance between the therapist and patient, and the findings of most studies are consistent across treatment modalities (Lebow et al., 2006; Najavits & Weiss, 1994). Such findings may provide another explanation for why evidence is limited regarding the differential effectiveness across these treatment modalities.

DURATION AND AMOUNT OF TREATMENT

When considering the evidence base for psychosocial treatments for SUDs, it is important to understand

the association between length of stay in residential programs and outcomes and the significance of continuing care for maintaining long-term reductions in substance use.

Length of Stay in Residential Treatment

Residential SUD treatment may be most appropriate for patients with greater substance use severity, significant psychiatric comorbidity, fewer social resources, and lower social competence (Drake et al., 2008; Finney, Moos, & Wilbourne, 2009; Rychtarik et al., 2000; Simpson, Joe, Fletcher, Hubbard, & Anglin, 1999; Tiet et al., 2007). However, the most appropriate length of stay in these programs is an issue of some debate. For example, naturalistic studies have found longer stays in residential SUD treatment programs to be associated with better patient outcomes (Moos & Moos, 1995; Simpson, Joe, & Brown, 1997), whereas type 1 and 2 trials (e.g., McCusker et al., 1997; Nemes, Wish, Messina, 1999) have tended to find that longer residential programs do not offer an incremental benefit over shorter programs (for reviews, see Mattick & Jarvis, 1994; Miller & Hester, 1986). Most recently, Harris and colleagues (2012) examined whether a longer average length of stay in SUD residential treatment programs in the U.S. Department of Veterans Affairs was associated with better substance-related outcomes. Compared to patients who were randomly selected from programs with an average length of stay of less than 90 days, those randomly selected from programs with an average length of stay greater than 90 days had a more extensive history of mental health treatment and were more likely to be homeless, but had fewer severe substance-related problems. Further, in covariate-adjusted analyses to examine outcomes after discharge, patients in programs longer than 90 days improved less on the alcohol composite of the Addiction Severity Index than patients from programs shorter than 90 days.

The discrepancy between naturalistic studies and randomized trials regarding the benefits of longer residential programs may be explained by the fact that, in naturalistic studies, certain patient characteristics are likely associated with better treatment retention (e.g., motivation to change), and that these characteristics (which are equated across groups in randomized trials) rather than the length of treatment itself lead to better outcomes. Alternatively, naturalistic studies may capture the dynamic interaction between patient characteristics and the effects of treatment that occur in real-world clinical settings; that is, patients with certain characteristics may stay in treatment longer and, as a result of receiving more treatment, may experience better outcomes. In any case, the predominantly null findings in randomized trials suggest that assigning patients to a longer planned duration of care, regardless of their level of motivation or other patient characteristics, will not lead to better outcomes. Rather, an individualized approach that considers patient preferences and allows patients to remain in treatment when they choose to and when clinically indicated is likely to lead to better outcomes.

Continuing Care Following Intensive Treatment

As defined by Blodgett and colleagues (2014), continuing care is "a period of less intensive treatment following a more intensive treatment episode" (p. 87), which is used to maintain and reinforce therapeutic gains. Due to the high rate of relapse among SUD patients, particularly within the first year after entering treatment (Jin et al., 1998), continuing care is a standard recommendation in guidelines for the treatment of SUDs (e.g., VA/DoD, 2009). The benefits of continuing care are supported by both naturalistic studies (Moos & Moos, 2003) and randomized trials (Dennis, Scott, & Funk, 2003; Sannibale et al., 2003). Further, in a number of randomized trials, telephone-based continuing care ("telephone monitoring") has been linked to improved outcomes (McKay et al., 2004, 2005, 2011; McKellar et al., 2012).

Three systematic reviews of the efficacy of continuing care have been conducted. First, McKay (2009) used a "box-score" approach to classify and count the number of trials that showed a positive (i.e., at least one significant effect on a primary substance use outcome) or negative (i.e., either no effect or a significant effect favoring the control condition) result for continuing care. A positive result was found in 10 of 20 trials, with positive results generally linked to a longer duration and greater intensity of care, as well as more active efforts to facilitate the delivery of continuing care (McKay et al., 2004, 2005). Similarly, Lenaerts and colleagues (2014) identified 20 trials of continuing care but focused on the 6 they found to be methodologically strong. The four that employed more

active interventions to empower patients seemed to have better drinking-related outcomes.

Blodgett and colleagues (2014) sought to expand upon prior box-score reviews by using meta-analytic techniques to calculate an overall effect size for the efficacy of continuing care and to conduct formal tests of potential moderators of this effect. Thirty-three controlled trials were identified, 19 of which compared continuing care to a no-treatment (or minimal-treatment) condition (total $n = 3{,}542$). In this subset of studies, a significant effect of continuing care was detected at the end of treatment (0.19), with a slightly larger effect at the last follow-up time point after the continuing care period (0.27). In terms of moderators, studies with longer planned durations of care or more sessions per week were not associated with a larger effect of continuing care at the end of treatment or at the last follow-up. CBT fared significantly better than other therapeutic modalities, although only in relation to a no-treatment control group. Studies using contracting, prompting, and social reinforcement to increase engagement in continuing care (e.g., Lash et al., 2007) did not demonstrate significantly larger effects than less active interventions; however, there was very little power to detect such effects, given the small number of such studies ($n = 3$). In addition, effect sizes in studies in which continuing care was delivered via telephone versus in-person did not differ, although it should be noted that the former approach is more cost-effective.

The findings of Blodgett and colleagues (2014) support the use of continuing care to facilitate and maintain recovery in patients with SUDs, although with some caveats. The overall effect of continuing care was relatively small and somewhat less impressive than the findings from naturalistic studies. However, this must be balanced with consideration of the advantages of naturalistic studies in terms of more accurately portraying real-world clinical settings. Further, in most studies, the amount of informal (e.g., mutual-help groups) or formal SUD care received by patients outside of the study was unclear, and in many cases participants assigned to a "no-treatment" control condition were given referrals to outside SUD care providers and mutual-help groups, which may have diluted the treatment effects for the continuing care conditions. Overall, the evidence supports an individualized approach to the provision of continuing care that relies primarily on cost-effective interventions (e.g., telephone monitoring) and considers a client's motivation, current functioning, and other resources and risk factors for relapse—all of which can be monitored through repeated assessments with validated instruments (i.e., measurement-based care; Cacciola et al., 2013; McKay, Drapkin, Goodman, & DePhilippis, 2009).

TREATMENT SETTING AND FORMAT

Due to their differences in cost, the relative effectiveness of residential and outpatient SUD treatment has been the focus of intense, but not rigorous, study (Reif et al., 2014). Finney, Hahn, and Moos (1996) conducted a box-score review of type 1 and 2 studies comparing the effectiveness of residential versus outpatient alcohol treatment. Five of 14 studies found a significant difference favoring residential care on one or more drinking outcomes, and in two other studies, day treatment was found to be superior to residential treatment. The remaining seven studies found no difference in patients' drinking outcomes as a function of setting. A meta-analysis of these studies by Finney and Moos (1996) detected a small, albeit significant, effect size at 3-month follow-ups that favored residential treatment settings; however, this effect was nonsignificant at 6- and 12-month follow-ups. Other randomized trials have observed few significant differences on drinking outcomes between patients assigned to residential versus outpatient SUD treatment (Greenwood, Woods, Guydish, & Bein, 2001; Guydish et al., 1999; Rychtarik et al., 2000; for a review, see McCarty et al., 2014) or between those assigned to day hospital versus residential programs (Witbrodt et al., 2007).

Importantly, individuals with greater SUD severity who are clinically judged to be in need of more intensive care cannot ethically be randomized to residential or outpatient treatment settings. Consequently, most studies have focused on patients who are less severely impaired and thus eligible for treatment in either setting. To address this issue, Finney and colleagues (1996) recommended a focus on large, multisite naturalistic studies to examine the relative efficacy of matching patients with greater substance use severity to more intensive residential treatment settings. In this vein, the American Society of Addiction Medicine has developed Patient Placement Criteria (Mee-Lee, 2013) to match patients to one of five levels of care: (a) early

intervention; (b) outpatient; (c) intensive outpatient/partial hospitalization; (d) residential/inpatient; and (e) medically managed inpatient treatment. Patients are matched on level of care based on ratings along six dimensions (acute intoxication or withdrawal potential; biomedical issues; emotional-behavioral issues; readiness for change; potential for relapse; and recovery environment).

Although the conceptual rationale for using these criteria appears compelling, they have received only limited empirical support (Finney, Moos, & Wilbourne, 2009; Magura et al., 2003). However, studies of patient/setting matching that did not specifically use—but were consistent with—these criteria suggest that more severely impaired patients (i.e., greater substance use severity, psychiatric severity, cognitive impairment; fewer social resources) tend to have significantly better outcomes if treated in residential settings (McKay et al., 2002; Rychtarik et al., 2000; Simpson et al., 1999; Tiet et al., 2007). Thus, a range of studies has demonstrated the value of matching patients to residential or outpatient care by considering their substance use severity, medical and psychiatric comorbidity and severity, level of cognitive functioning, and social resources and recovery environment.

Another important issue, particularly from the standpoint of cost, is the relative effectiveness of group versus individual treatment. The majority of psychosocial treatments for SUDs have used group therapy as the primary mode of delivery (Walters, Ogle, & Martin, 2002), although the efficacy of this approach relative to individual therapy has been tested in only a handful of studies. In a review by Weiss and colleagues (2004), four randomized trials were identified that focused on a specific treatment modality. In all four studies, the primary substance use outcomes showed significant reductions as a function of treatment, but the outcomes did not differ between group and individual formats. (Of note, it is unclear whether these studies accounted for the clustering of patients within groups in the analyses; see Morgan-Lopez, Cluff, & Fals-Stewart, 2009.) In addition, a recent trial of a CBT-based MI intervention found significant reductions in patients' substance use outcomes during treatment and at a 12-month follow-up, but no significant differences between the group and individual conditions in the outcomes at either time point (Sobell et al., 2009). From a cost containment standpoint, these findings suggest that health care systems may obtain the most "bang for their buck" by providing SUD treatment in a group format.

MATCHING PATIENTS TO PSYCHOSOCIAL TREATMENT MODALITIES

There is some support for matching patients with SUDs to specific psychosocial treatment modalities to maximize the effectiveness of treatment. For example, patients with chronic SUDs marked by severe psychiatric comorbidity responded better to highly structured CBT-based approaches (Rosenblum et al., 2005), whereas those with less psychiatric severity and more adaptive coping styles fared better with less structured and more facilitative interventions (Gottheil et al., 2002). Other work has suggested that patients with fewer social or personal resources improve more when they receive treatments that explicitly target those deficits. For example, relative to patients with more support from family or friends (e.g., married patients), those with an underdeveloped social support network benefit more from CRA-based approaches, which aim to augment patients' support networks (Azrin, Sisson, Meyers, & Godley, 1982). Further, CBT may be better suited than MI for patients who have trouble expressing their feelings (Rosenblum et al., 2005). However, CBT requires a moderate level of cognitive functioning, and some evidence suggests that individuals with cognitive impairments benefit less from coping skills training due to difficulties in learning and recalling new information (Maude-Griffin et al., 1998; Smith & McCrady, 1991).

Their promise notwithstanding, it is important to note that the findings of these studies were based largely on exploratory analyses. Further, a review of 54 alcohol treatment studies found that 22% of the variance in the number of significant patient/treatment interaction effects could be accounted for by the number of tests of interaction that were conducted (Moyer, Finney, Elworth, & Kraemer, 2001). These limitations emphasize the need for studies designed to test a priori matching hypotheses. To date, three such major studies have been conducted. Most notably, Project MATCH compared patients randomly assigned to CBT, MET, and TSF and tested 16 matching hypotheses that had both theoretical and empirical support. Of a total of 64 contrasts tested, only one was statistically significant (Project MATCH

Research Group, 1997). Similarly, no evidence for matching effects was detected in tests of matching hypotheses in the UKATT study of MET and social network therapy (UKATT Research Team, 2005) or in the VA Effectiveness Study of programs with a CBT and/or TSF orientation (Ouimette et al., 1999).

Although the findings of these multisite trials are not encouraging, limitations in their methodological design suggest that patient/treatment matching effects may still be present. For example, all three treatment modalities in Project MATCH were delivered in an individual format on an outpatient basis and therefore may not have been as distinct as would be preferred in a treatment-matching study. This fact is notable, given the earlier-cited evidence supporting matching patient severity to treatment settings, and other evidence supporting matching supplementary services to other concurrent needs of SUD patients (e.g., social and employment domains; Friedmann et al., 2004; McLellan et al., 1997, 1998). In addition, reexamination of Project MATCH data using growth mixture modeling provided partial support for three a priori matching hypotheses: (1) patients low on self-efficacy at baseline had better posttreatment outcomes if assigned to CBT than MET (Witkiewitz et al., 2007); (2) patients with higher network support for drinking at baseline fared better if assigned to TSF than either CBT or MET (Wu & Witkiewitz, 2008; see also Longabaugh, Wirtz, Zweben, & Stout, 1998); and (3) patients with lower motivation to change at baseline had better outcomes if assigned to MET relative to CBT (Witkiewitz et al., 2010).

More recent secondary analyses also suggest moderate support for some patient/treatment matching effects. For example, several studies by Karno and colleagues (2005a, 2005b, 2009) found significant matching effects based on patients' interpersonal style and therapist characteristics using Project MATCH data. Specifically, patients higher on anger and reactance who had more directive and structured therapists generally had poorer drinking outcomes, whereas those lower in reactance fared better with highly directive therapists. These findings were replicated in a sample of patients dependent on methamphetamine who were randomly assigned to directive and nondirective telephone aftercare (Karno et al., 2012). In addition, a recent study found that adults with SUDs who were depressed and had poor neuropsychological functioning fared better in CBT than TSF groups, possibly because they needed formal structured training to develop and use novel coping skills (Granholm et al., 2011; but see Maude-Griffin et al., 1998; Smith & McCrady, 1991).

LIMITATIONS OF EXISTING RESEARCH

Several limitations must be considered when interpreting the existing research literature. Most importantly, our conclusions regarding the SUD treatment modalities with the most empirical support are based, in part, on the results of box-score reviews, which calculate the proportion of relevant studies that have found a significant treatment effect for a given modality in comparison to some alternative condition. These reviews preceded, and were not designed to meet, the Institute of Medicine's standards of systematic reviews (National Research Council, 2011). For example, they lack a standard treatment condition against which various treatment modalities can be compared (see Finney, 2000). For example, if two highly effective psychosocial treatment modalities are frequently compared to each other, each modality would be deemed "ineffective" using a box-score review approach. Consequently, reliance on only box-score reviews can distort the evidence for the relative efficacy of a given modality (see our earlier discussions regarding TSF).

Statistical and methodological issues also pose challenges. First, variation in statistical power to detect treatment effects can distort the findings of box-score reviews as it may contribute to a null finding in studies with small samples but a statistically significant treatment effect of the same size in a larger study. Notably, Moyer, Finney, and Swearingen (2002) reported that, given the lower power of alcohol treatment trials published from 1970 to 1998, there was, on average, just over a 50-50 chance of detecting a statistically significant, medium-sized treatment effect, assuming one test of an effect. Second, most trials in the SUD treatment literature have examined multiple outcome variables assessed across multiple follow-up points, which increases the risk of type 1 error. This situation is especially problematic in box-score reviews, given that there is rarely a correction for the number of tests conducted; thus, studies that include multiple comparisons may conclude that a given treatment modality is efficacious based on a chance finding. Third, as highlighted by Baldwin, Murray, and Shadish (2005), most studies of SUD treatments administered in a group format have not accounted for violations of the

assumption of independence, which also increases the risk of type 1 error.

Despite their limitations, box-score reviews can reveal important patterns, particularly when (a) they are based on a large number of studies, (b) they address a clear question with reference to participants, interventions, comparisons, outcomes, and study design, and (c) efforts are made to quantify and adjust for the quality of the included study designs. As an alternative to box-score reviews, meta-analyses can provide effect sizes to determine not just the statistical significance of a given study but the overall magnitude of an average treatment effect across studies. Such analyses are less likely to be biased by studies of low power or multiple comparisons and also have the ability to examine moderators of treatment effects to determine the conditions under which a given treatment modality is more or less efficacious. For example, meta-analyses can examine the magnitude of a given modality's treatment effect in comparison to no-treatment controls, as well as other active control conditions (for an example, see Magill & Ray, 2009).

Beyond the limitations of box-score reviews, other factors present challenges to integrating the findings across randomized trials of psychosocial treatments for SUDs. For example, relatively little is known about the representativeness of patients who are enrolled in the existing trials. This is partly due to the fact that most studies do not report the proportion of patients screened who were eventually enrolled into a trial (Gross, Mallory, Heiat, & Krumholz, 2002). Melberg and Humphreys (2010) conducted a systematic review of 98 clinical trials from the drug dependence literature and reported that, on average, 29% of potential subjects were ineligible and an additional 29% refused to participate. These rates were even higher in larger trials, suggesting that the benefits of greater power from such studies may be offset by the possibility of bias in the sample selected. Such bias may be less relevant if the characteristics of patients who enrolled are comparable to those who are ineligible or unwilling to participate. However, only 6% of the studies Melberg and Humphreys (2010) reviewed provided such information, and they tended to lack sufficient power to detect such differences (see also Humphreys et al., 2013).

A related issue is the representativeness of patients who complete follow-up assessments in randomized trials. A recent review of 24 studies found that younger patients were less likely than older patients to be retained in clinical trials (Korte et al., 2011). To address these potential biases, greater transparency is needed about the population from which participants are recruited and how differences in retention at follow-ups across subgroups of participants may affect the interpretation of study findings. Greater adherence to the Consolidated Standards of Reporting Trials (CONSORT; Boutron et al., 2008) is one method to address this issue, as well as appropriate handling of missing data in analyses (Hallgren & Witkiewitz, 2013).

Another limitation is the variability across studies in the outcomes used to determine whether a treatment is efficacious, as well as in the most appropriate methods of assessing these outcomes. A panel of treatment and research experts recently concluded that substance use behavior should ideally be measured by a combination of self-report and biological indicators (e.g., urine analysis). However, the panel also acknowledged that the most appropriate outcome will inevitably vary as a function of a number of variables, including the specific type of intervention and its treatment goals (e.g., abstinence or harm reduction) and that a formal decision process is needed to guide researchers in the selection of the most appropriate primary and secondary outcomes and methods of assessment (Donovan et al., 2012). For clinical trials of alcohol use treatments, some consensus has emerged for use of "percent of subjects with no heavy drinking days" as an efficacy endpoint (Falk et al., 2010).

Finally, better integration of findings across randomized trials of psychosocial treatments for SUDs would be aided greatly by more consistent standards of reporting the findings from trials. The CONSORT was developed precisely for these purposes, and an analysis by Ladd and colleagues (2010) showed that the quality of reporting alcohol treatment outcomes has improved more in studies published in journals that adopted the CONSORT guidelines. Thus, efforts to enforce consistent reporting of the findings of type 1 and 2 SUD treatment trials using these guidelines may help address many of the key issues identified in methodological reviews of this literature.

WHAT WORKS IN SUBSTANCE USE DISORDER TREATMENT

Findings from meta-analyses and type 1 and type 2 RCTs indicate that the most efficacious and

effective psychosocial modalities for treating SUDs are cognitive-behavioral interventions, MI/MET, CM and CRA (particularly when combined), behavioral couples and family therapies, and TSF approaches. Limited evidence is available on the differential effectiveness of these interventions. With the exception of CM, the evidence for effectiveness is stronger for the treatment of alcohol (vs. drug) use disorders (VA/DoD, 2009). Regardless of modality, therapists who are interpersonally skilled, empathic, and less confrontational tend to establish stronger alliances with patients, which in turn lead to better patient outcomes.

These general conclusions are highly congruent with the conclusions reached in the previous version of this chapter, which was published in 2007. This may be due to the fact that systematic comparisons of psychosocial treatments for SUDs are still limited to box-score and qualitative reviews. Future efforts to systematically compare the most common psychosocial treatment modalities should conform to the recommendations of the Institute of Medicine (National Research Council, 2011). In addition, research on mechanisms of change (which has grown considerably since the last version of this chapter) suggests that effective interventions operate more or less through common social processes (i.e., increasing support, goal direction, and structure for patients; increasing engagement in activities and rewards that can substitute for alcohol and drug use; increasing exposure to abstinence-oriented norms and models; and developing patients' coping skills and increasing their self-efficacy). Thus, it may be expected that there will be fewer advances in this area in terms of identifying novel psychosocial treatments that are as effective as (or more so) than existing modalities.

These similar conclusions notwithstanding, there have been a number of important advances in this literature over the past 7 years. First, the evidence base for brief interventions has grown considerably, particularly within primary care. However, as a stand-alone intervention, the efficacy is still limited to the treatment of mild to moderate alcohol use problems; more intensive residential programs are best suited for patients with greater substance use severity, limited social resources, and significant psychiatric and medical comorbidity. Second, there are now a number of meta-analyses to support the efficacy of computer- and Web-delivered interventions. Such interventions will greatly increase the ability to provide care to individuals from rural areas; however, extant studies have been limited to treatment of hazardous drinking among college students. Third, several recent studies indicate that therapist variability is primarily responsible for alliance–outcome associations; this highlights the potential value of increased supervision and monitoring of therapists to maximize treatment outcomes. Fourth, in contrast to earlier literature on duration and amount of care, the most recent work supports an individualized approach marked by variable intensity of continuing care and ongoing monitoring of functioning and risk (i.e., measurement-based care). Fifth, although this chapter focused exclusively on psychosocial treatments for SUDs, the most recent work suggests that these modalities may be limited for individuals with more severe SUDs and should therefore be used in conjunction with pharmacotherapies (Anton et al., 2006; Oslin et al., 2014; VA/DoD, 2009).

Finally, an ongoing challenge for the field is to determine how best to implement efficacious interventions for SUDs into real-world clinical settings so that they are cost-effective; can reach the patient population in most need of the intervention; produce positive outcomes; are adopted by clinical providers; are delivered as intended or adapted in a way that does not compromise the integrity of the treatment; and are integrated into routine practice and maintained over the long term (Glasgow et al., 1999). Examining these issues should help identify factors associated with successful implementation of empirically supported treatments for SUDs (Lash et al., 2011; Manuel, Hagedorn, & Finney, 2011).

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24

Psychopharmacological Treatments for Substance Use Disorders

James R. McKay
Henry R. Kranzler
Kyle M. Kampman
Rebecca L. Ashare
Robert A. Schnoll

The treatment of substance use disorders (SUDs) with medications is well established, although most experts agree that, to be successful, pharmacological interventions must be combined with psychosocial therapies. A large number of type 1 and type 2 controlled trials have shown that the use of nicotine replacement therapy (NRT) to induce and maintain smoking cessation significantly increases abstinence rates. Non-nicotine treatments, such as bupropion, which is also an antidepressant, and varenicline, have been found in controlled trials to significantly increase smoking abstinence rates measured at intervals up to 12 months after the beginning of treatment. The treatment of alcohol use disorder can now be enhanced by three approved medications that are based on different mechanisms of action: disulfiram, an aversive agent that works when adherence is assured; naltrexone, which reduces alcohol reward via the endogenous opioid system and results in decreased alcohol craving and reduced heavy drinking; and acamprosate, which reduces post-alcohol excitability and has been effective in European trials but not in U.S. or Australian trials. A long-acting version of naltrexone has been approved by the U.S. Food and Drug Administration (FDA) to treat alcohol and opiate dependence. It provides therapeutic blood levels for at least 30 days and may improve adherence, which is an important consideration in the treatment of SUDs. Methadone maintenance treatment has consistently shown efficacy in the treatment of opioid dependence, and the partial opioid agonist buprenorphine has substantially expanded the options for treating the disorder. Buprenorphine is available to treat opioid addiction by qualified physicians in their offices rather than being dispensed only in a highly regulated treatment program, as is required for methadone. There are as yet no FDA-approved medications to treat addiction to stimulants, which include cocaine and methamphetamine. Although double-blind, placebo-controlled clinical trials of several medications have provided initial evidence of efficacy to treat cocaine use disorder, they have not yet been shown in multisite trials to be efficacious.

INTRODUCTION

SUDs affect virtually every sector of society. As a group they are among the most common of all mental disorders. Household surveys have found a lifetime prevalence rate of 15% to 18% and a 12-month prevalence rate of 9% (Cohen, Feinn, Arias, & Kranzler, 2007; Grant et al., 2004; Kessler et al., 2005). These rates do not include nicotine addiction, one of the most devastating and difficult to treat of all the addictive disorders. Although rates of cigarette smoking in the United States have declined, smokers unable to quit on their own are among the most difficult patients presenting for treatment. Many individuals have multiple addictions; for example, alcoholics frequently are addicted to both cocaine and nicotine. There is also a good deal of overlap with other mental disorders such as anxiety and mood disorders.

There are common properties among the disorders produced by the major drugs of abuse, but there are also important differences, particularly in treatment approaches. Thus, a chapter on treatment of SUDs must consist of four distinct reviews focusing on the major drugs or drug categories: nicotine, alcohol, stimulants (cocaine, methamphetamine), and opioids (heroin and prescription opioids). Other drugs, such as cannabinoids, hallucinogens, Ecstasy, and minor tranquilizers, may also be abused, but they account for a relatively small proportion of patients needing treatment, and there are no effective medications currently available.

The features that define SUDs include compulsive use of the substance despite interference with normal activities and adverse effects on health. The recent publication of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*; American Psychiatric Association, 2013) reflects a substantial modification in the diagnosis of SUDs. In contrast to *DSM-IV*, *DSM-5* does not differentiate between abuse and dependence. Rather, based on findings that the *DSM-IV* abuse criteria aggregate with the criteria for dependence, *DSM-5* SUD criteria incorporate both abuse and dependence criteria. Specifically, there are 11 criteria: three of the four *DSM-IV* abuse criteria (legal problems having been omitted due to low frequency of endorsement), seven dependence criteria, and craving. Mild SUD is present when two or three criteria are met in a 12-month period; moderate SUD is diagnosed when four or five criteria are present; and the diagnosis of severe dependence is made when 6 to 11 criteria are met.

SUCCESS OF TREATMENT

In this chapter we define successful treatment as significant reductions in substance use and negative consequences of use, along with improvement in the ability to function according to one's societal role. Total abstinence from the addictive substance is often the accepted goal of treatment, but this is not often achieved. In the case of opioid addiction, transfer to a stable maintenance medication, albeit pharmacologically similar in many ways to heroin, is considered successful treatment provided that the person can refrain from socially and personally harmful behavior. This definition of success is commonly used for other chronic disorders such as arthritis or diabetes; it therefore is a pragmatic and medically acceptable definition based on functional capacity.

DETOXIFICATION

Detoxification is simply the removal of a drug from the body. This usually occurs because of metabolism by the liver and excretion via the kidneys. If the intake of the drug is gradually decreased, detoxification can be accomplished with little risk or discomfort as the body adapts to the absence of the drug. Detoxification is often confused with treatment, but in reality detoxification is, at best, the first step in treatment. Detoxification from sedatives such as alcohol can be dangerous because of medical complications during withdrawal, but these are readily treated in any medical facility and in the vast majority of cases on an outpatient basis. Treatment of the addiction involves a process of rehabilitation to reduce the probability of relapse and lengthen the time that the person is no longer using the drug of abuse. There is no evidence that rapid detoxification under general anesthesia is any more effective in the long term than less heroic and expensive means. Although some interesting research has been done on novel ways to achieve detoxification, for the purposes of this chapter we will emphasize long-term, relapse prevention or harm reduction treatment.

PSYCHOACTIVE AGENTS IN THE TREATMENT OF ADDICTION

One might reasonably ask whether medications are ever justified in the treatment of a disorder that involves excessive use of drugs. Although there is controversy about this on philosophical grounds, empirical studies clearly show the benefits of medications when they are indicated. In addition to the treatment of the addictive disorder itself, psychoactive medications are often indicated to treat accompanying psychiatric disorders. One school of thought that had many proponents in the past was that addicts were all more or less alike and all had to be treated by "getting at the underlying problem" and insisting on strict freedom from all drugs. In that earlier era, nicotine and caffeine were not usually thought of as drugs, but all psychoactive medications prescribed by physicians were avoided. Subsequent data, however, have demonstrated that all addicts are not alike. Even within a single drug category such as alcohol, dependent individuals have different needs that require different kinds of treatment. Heredity also has a major influence on the risk of addiction, and data indicate that treatment response is also influenced by genetic variation (Johnson et al., 2011, Kranzler et al., 2014; Oslin et al., 2003). The concept of patient/treatment matching, now referred to as personalized medicine, has become popular despite a relative paucity of replicated, empirical findings.

NICOTINE DEPENDENCE

Cessation of smoking may be very difficult even for smokers who strongly desire to quit, and subsequent resumption of smoking, despite long periods of abstinence, is common. Those who begin smoking prior to age 21 are less likely to succeed in smoking cessation programs. Most smokers are nicotine dependent and experience a variable withdrawal syndrome when regular administration of nicotine is stopped. The nicotine withdrawal syndrome consists of irritability, impatience, hostility, anxiety, dysphoric or depressed mood, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain.

Nicotine administration can block these withdrawal symptoms whether given intravenously, by absorption though the mucosal membranes of the mouth (chewing gum or sucking a lozenge), by absorption through the skin (patch), via nasal spray, or by an inhaler or an electronic cigarette. Although the peak nicotine levels associated with the psychoactive effects of smoking are not achieved by chewing gum or by patch administration, their widespread availability as over-the-counter medications has enabled many smokers to avoid the serious health risks of tobacco smoke. Most smokers can then gradually reduce their nicotine dependence over several days to weeks. Craving for the psychoactive effects continues, however, and relapses to smoking over the ensuing months are common. Table 24.1 summarizes clinical trial results for NRT. Meta-analyses demonstrate efficacy for nicotine patch, gum, inhaler, lozenge, and nasal spray, and quit rates are increased with higher dose of nicotine gum, the use of combination NRTs, and the use of NRT with the non-nicotine medication bupropion (Stead et al., 2012). Despite substantial interest in electronic cigarettes, the first randomized controlled trial (RCT) showed no significant increase in cessation rates compared to nicotine patch or placebo electronic cigarette (Bullen et al., 2013).

The association of smoking and depression has led to the evaluation of several classes of antidepressants as potential treatments for nicotine dependence, including selective serotonin reuptake inhibitors and monoamine oxidase inhibitors. Meta-analyses indicate that bupropion, an atypical antidepressant, significantly improves cessation rates compared to placebo (Table 24.2; Hughes, Stead, & Lancaster, 2007), but it is not significantly more efficacious than NRT (Cahill, Stevens, Perera, & Lancaster, 2013). It is equally effective for treating nicotine addiction with or without a history of comorbid depression, but may be less effective for smokers with current depression (van der Meer, Willemsen, Smit, Cuijpers, & Schippers, 2013). In addition, the tricyclic antidepressant nortriptyline, has been found to significantly increase cessation rates compared to placebo (see Table 24.2; Cahill et al., 2013; Hughes et al., 2007), although this medication is not currently FDA approved for treating nicotine dependence.

Most recently, varenicline, a nicotinic receptor partial agonist, was approved for treating nicotine dependence by the FDA. As a partial agonist it reduces withdrawal symptoms by maintaining moderate dopamine levels, and as an antagonist it blocks the rewarding effects of smoking. Two seminal placebo-controlled studies demonstrated the efficacy of varenicline (Gonzales et al., 2006; Jorenby et al.,

TABLE 24.1 Treatment of Nicotine Use Disorder: Nicotine Replacement Therapy (NRT)

Authors	*Study Class*	*N, Number of Studies*	*Treatment Length*	*Follow-up Length*	*Results*		*Comments and Dosing*
Stead et al. (2012)	4	>50,000; 150 studies	3 weeks or longer	6 months or longer	Randomized Controlled Trials		Comprehensive review, including each NRT and a range of moderating variables.
					Treatment	Risk Ratio (95% CI)	
		19,586; 43			Nicotine patch	1.64 (1.52–1.78)	7–21 mg (depending on amount smoked) daily for 8–10 weeks starting on quit day; use patch 16–24 hours each day.
		22,581; 56			Nicotine gum	1.49 (1.40–1.60)	2 mg (if your first cigarette of the day is typically 30 minutes or more after waking) or 4 mg (if your first cigarette of the day is typically <30 minutes of waking); use at least 9 pieces per day for the first 6 weeks and then taper use; use for up to 12 weeks.
		3,405; 7			Nicotine lozenge	1.95 (1.61–2.36)	2 mg (if your first cigarette of the day is typically 30 minutes or more after waking) or 4 mg (if your first cigarette of the day is typically <30 minutes of waking); use >9 lozenges/day for 6 weeks then taper use; use for up to 12 weeks.
		976; 4			Nicotine inhaler	1.90 (1.36–2.67)	Use 6–16 cartridges/day for up to 6 months with dose taper for final 3 months.
		887; 4			Nicotine nasal spray	2.02 (1.49–2.73)	Use 8–40 doses/day for 3–6 months.
		618; 4			High-dose gum[a]	1.85 (1.36–2.50)	4 mg for 12 weeks.
		4,664; 9			Combination NRT[b]	1.34 (1.18–1.51)	See above.
		1991; 4			NRT and bupropion	1.24 (1.06–1.45)	See above and Table 24.3.
Bullen et al. (2013)	1	657; 1			E–cigarette (vs. patch; vs. placebo)	1.26 (0.68–2.34) 1.77 (0.54–5.77)	First randomized trial to compare e-cigarette to nicotine patch and placebo e-cigarette.

[a] In highly dependent smokers only; [b] Two NRTs vs. one.

TABLE 24.2 Treatment of Nicotine Use Disorder: Antidepressants

Authors	*Study Class*	*N, Number of Studies*	*Treatment Length*	*Follow-up Length*	*Results*		*Comments and Dosing*
Hughes et al. (2007)	4	>13,000; 66 studies	3 weeks or longer	6 months or longer	Randomized Controlled Trials		Comprehensive review of numerous classes of antidepressants, assessment of side effects and adverse events, and comparisons to nicotine replacement therapy and varenicline.
					Treatment	Odds Ratio (95% CI)	
		>11,000; 36			Bupropion	1.69 (1.53–1.85)	Begin dosing 1–2 weeks before quit date; 150 mg/day for days 1–3; 300 mg/day for days 4–7 and for an additional 6–11 weeks. Additional weeks may be considered for successful quitters.
		975; 6			Nortriptyline	2.03 (1.48–2.78)[a]	75–100 mg/day or titrated to pre-quit serum levels recommended for depression for 60 days to 12 weeks.
		1,622; 3			Vs. Varenicline	0.66 (0.53–0.82)[b]	See above and Table 24.3.

[a] Excluded one trial considered to have inadequate methodological rigor; [b] Trials used bupropion.

TABLE 24.3 Treatment of Nicotine Use Disorder: Nicotine Receptor Partial Agonists

Authors	*Study Class*	*N, Number of Studies*	*Treatment Length*	*Follow-up Length*	*Results*		*Comments and Dosing*
Cahill et al. (2012)	4	10,666; 24 studies	3 weeks or longer	6 months or longer	Randomized Controlled Trials		Comprehensive review, including three medications, assessment of side effects and adverse events, and comparisons to nicotine replacement therapy and bupropion.
					Treatment	Odds Ratio (95% CI)	
		6,166; 14			Varenicline	2.27 (2.02–2.55)	Begin dosing 1 week before quit date; 0.5 mg once daily on days 1–3, 0.5 mg twice daily on days 4–7, and 1 mg twice daily for 11 weeks; 12 additional weeks for successful quitters.
		2,151; 3			Cytisine	3.98 (2.01–7.87)[a]	1.5 mg/day for 20–25 days.
		1,622; 3			Vs. Bupropion	1.52 (1.22–1.88)[b]	See Table 24.2.
		1,272; 4			Low-dose varenicline	2.09 (1.56–2.78)	0.3 mg daily; 1.0 mg daily; 0.5 mg twice daily; or 0.5 mg 1–4 times per day.

[a] Excluded one trial considered to have inadequate methodological rigor; [b] Trials used varenicline.

2006). Since then, more than a dozen studies have shown that smokers taking varenicline are more than twice as likely to be abstinent at a 6-month follow-up, compared to placebo (Table 24.3; Cahill, Stead, & Lancaster, 2012). Varenicline is more efficacious than NRT and bupropion (Cahill et al., 2013), possibly by more effectively reducing craving and reinforcement from smoking (Cinciripini et al., 2013). The efficacy of varenicline at a reduced dose has also been demonstrated (Cahill et al., 2012). While the FDA labeling for varenicline includes a warning about the potential neuropsychiatric and suicide risks associated with this medication, several large studies indicate that the varenicline is a safe medication for treating nicotine dependence (Buggy et al., 2013; Gibbons & Mann, 2013).

Lastly, another nicotinic receptor partial agonist, cytisine, has been shown to be an effective treatment for nicotine dependence in two trials (Cahill et al., 2012, 2013).

Ongoing research is focused on improving the efficacy of existing treatments by identifying individual predictors of treatment response. The rate at which nicotine is metabolized by the cytochrome P450 (CYP) 2A6 enzyme has been shown to be stable across time and predictive of smoking relapse. Fast metabolizers of nicotine smoke more cigarettes, are more nicotine dependent, have more difficulty quitting, and have a worse response to nicotine patch treatment compared to slow metabolizers (Lerman et al., 2006; Schnoll et al., 2009). However, bupropion has been shown to be more effective among fast metabolizers (Patterson et al., 2008). Current clinical trials investigating the use of this biomarker of nicotine metabolism may offer an innovative approach to personalizing treatment for nicotine dependence, thereby enhancing the efficacy of these medications.

ALCOHOL USE DISORDER

Medications that have been evaluated to treat alcohol use disorder include aversive agents; serotonergic medications, including antidepressants, anxiolytic agents, and the serotonin-3 receptor (5-HT3) antagonist ondansetron; and agents that are intended to block the effects of alcohol at the neurotransmitter level, including opioid antagonists and the anticonvulsant medication topiramate (Kranzler et al. 2013). The most recent approval of medications to treat alcohol dependence in the United States was in 2006, when the FDA approved a long-acting injectable formulation of naltrexone. Studies of these agents are described in detail in a number of reviews or meta-analyses, which are cited in the sections that follow.

Aversive Medications

Aversive medications produce an unpleasant reaction when alcohol is consumed, which is intended to deter drinking. Disulfiram, the only aversive medication approved to treat alcoholism in the United States, has long been used in alcohol rehabilitation (Favazza & Martin, 1974). Consuming alcohol following the ingestion of disulfiram causes an elevated plasma concentration of acetaldehyde, resulting from disulfiram's blockade of the catabolism of acetaldehyde, a metabolite of alcohol. The intensity of the reaction varies both with the dose of disulfiram and the volume of alcohol consumed.

Overall, disulfiram is no more effective than placebo in promoting abstinence (Suh, Pettinati, Kampman, & O'Brien, 2006). The largest and most methodologically rigorous study of disulfiram was a 1-year multicenter trial in which more than 600 male veterans with alcohol dependence were randomly assigned to receive disulfiram (at a dosage of either 1 mg/day or 250 mg/day) or an inactive placebo (Fuller et al., 1986). Patients assigned to the two disulfiram groups were told they were being given the drug, but neither patients nor staff knew the dosage. Irrespective of the medication group, patients who were adherent to the medication and treatment visit regimen were more likely to remain abstinent throughout treatment. In a planned secondary analysis of patients who resumed drinking, the group that received the approved dosage of disulfiram (i.e., 250 mg/day) reported significantly fewer drinking days than patients in the other two groups. Thus, disulfiram may help to reduce the frequency of drinking in men who cannot maintain abstinence (Fuller et al., 1986).

Disulfiram may be more effective in preventing relapse when combined with efforts to enhance medication adherence (e.g., by contracting with the patient and a significant other to work together to ensure adherence, providing the patient with regular reminders and other information, incentives, and behavioral training and social support) (Allen & Litten, 1992; Brewer, Meyers, & Johnsen, 2000). Azrin

and colleagues (1982) found that disulfiram-treated patients who received a trial program of stimulus control training, role-play, communication skills training, and recreational and vocational counseling had better outcomes than those receiving placebo. Chick and colleagues (1992) randomly assigned patients to receive disulfiram 200 mg/day or placebo for 6 months as an adjunct to outpatient alcoholism treatment. The patient ingested the study medication under the supervision of an individual nominated by the patient. Disulfiram treatment significantly increased abstinent days and decreased total drinks consumed, with parallel changes in levels of the hepatic enzyme gamma-glutamyltransferase (GGT).

Disulfiram is administered orally. Because of the risk of side effects and toxic reactions, the daily dosage prescribed in the United States has been limited to 250 to 500 mg/day. However, efforts to titrate the dosage of disulfiram in combination with a challenge dose of ethanol indicate that in some patients more than 1 g/day of disulfiram is required to produce a disulfiram–ethanol reaction (Brewer, 1984).

The adverse effects of disulfiram, particularly the potential for the disulfiram–ethanol reaction, contraindicate its use in patients with a variety of medical and psychiatric conditions and in pregnant women. Prior to initiation of therapy, the potential for disulfiram to cause a reaction when combined with alcohol should be discussed openly with the patient. The disulfiram–ethanol reaction commonly includes sweating, flushing, hyperventilation, thirst, nausea, vomiting, palpitations, tachycardia, vertigo, and weakness, although more severe symptoms, including syncope and, rarely, cardiovascular collapse, have also been reported. To prevent precipitating an adverse reaction, the patient should also avoid over-the-counter preparations with alcohol, foods prepared with alcohol, and drugs that can interact with disulfiram.

The following tests are recommended by the Center for Substance Abuse Treatment (2009) before initiating disulfiram therapy: liver function tests (alanine aminotransferase, aspartate aminotransferase, GGT, alkaline phosphatase, lactate dehydrogenase, bilirubin, total protein, albumin, and prothrombin time), complete blood count, blood urea nitrogen, serum creatinine, and a pregnancy test for women of reproductive potential. Liver function tests should be repeated 10 to 14 days after beginning treatment, monthly for the first 6 months of therapy, and then at 3-month intervals thereafter, and pregnancy testing should be repeated monthly during treatment.

Serotonergic Agents

Serotonin plays an important role in the modulation of mood and impulse control and appears to influence the development and maintenance of alcohol use disorders (Kranzler & Anton, 1994). Because studies have suggested that individuals with alcohol use disorders may have low levels of serotonin (Kranzler & Anton, 1994), a number of serotonergic medications have been evaluated as treatments for alcohol dependence. The agents that have received the greatest attention are serotonin reuptake inhibitors (SRIs), such as citalopram and sertraline, and ondansetron, a 5-HT3 receptor antagonist. Although studies of SRIs indicate that these agents may lead to short-term reductions in alcohol consumption in heavy drinkers, studies in alcohol-dependent patients have yielded mixed findings (Kranzler et al., 2013). Overall, the only clear justification to use SRIs to treat alcohol dependence is in late-onset alcoholics (i.e., with onset after age 25), for which some support exists (Kranzler et al., 2011; Pettinati et al., 2000), or those with co-occurring depression, who appear to respond to sertraline treatment when combined with naltrexone (Pettinati et al., 2010), but not as monotherapy (Kranzler et al., 2006).

The efficacy of ondansetron has been examined in several studies. Johnson and colleagues (2000) showed that it reduced drinking behavior only among early-onset alcoholics (onset of problem drinking before age 25). At a dosage of 4 μg/kg twice daily—substantially lower than its antiemetic dosage—ondansetron increased the proportion of days abstinent and reduced the intensity of drinking more than placebo. In contrast, in late-onset alcoholics, ondansetron's effects on drinking behavior were no better than those of placebo.

A subsequent study by Johnson and colleagues (2011) showed that the effects of ondansetron were not moderated by the age of onset of problem drinking. Rather, in this study, the medication reduced drinking only in alcoholics homozygous for the L allele of a polymorphism (5-HTTLPR) in *SLC6A4*, the gene encoding the serotonin transporter. Further, a single nucleotide polymorphism (SNP) in the 3′ untranslated region (3′UTR) of the gene (Seneviratne

et al., 2009) interacted with the 5-HTTLPR polymorphism to moderate the response to ondansetron. Thus, ondansetron reduced drinking most in individuals with the LL genotype at 5-HTTLPR and the TT genotype of the 3′UTR SNP. Recently, Johnson and colleagues (2013), in a secondary analysis of this study, found that polymorphisms in the genes encoding the 5-HT3 receptor, *HTR3A* (rs1150226 and rs1176713) and *HTR3B* (rs17614942), also moderated the response to ondansetron. In patients selected for specific genotypes at these loci (more than one third of those originally enrolled), ondansetron exerted moderate to large effects on drinks per drinking day, the percentage of heavy drinking days, and the percentage of days abstinent. If replicated, these findings would contribute substantially to the personalization of alcohol dependence treatment by allowing medication to be selected based on genotypic information obtained prior to the initiation of treatment, thereby offering a high likelihood of a favorable treatment response.

Opioid Antagonists

Two opioid antagonists have been shown to be efficacious in the treatment of alcohol dependence (Table 24.4).

Naltrexone

In 1994, the FDA approved naltrexone to treat alcoholism based on two single-site clinical trials (O'Malley et al., 1992; Volpicelli et al., 1992). Most, but not all, subsequent placebo-controlled studies of naltrexone have shown it to be efficacious in alcohol treatment. Of note is the COMBINE study, a placebo-controlled trial that compared naltrexone, acamprosate, and the two medications combined, together with either medical management or an intensive psychotherapy, in a sample of 1,383 subjects (Anton et al., 2006). Naltrexone, when combined with medical management, modestly reduced the risk of heavy drinking and modestly increased the percent days abstinent, effects that were not enhanced by the addition of an intensive cognitive-behavioral intervention.

Meta-analyses conducted over more than a decade (Bouza et al., 2004; Kranzler & Van Kirk, 2001; Rösner et al., 2010b; Srisurapanont & Jarusuraisin, 2005) have consistently shown naltrexone to be efficacious, principally in reducing the risk of heavy drinking. The most recent of these meta-analyses (Rösner et al., 2010b) included a total of 50 RCTs with nearly 8,000 participants. It showed that naltrexone produced a modest, statistically significant reduction (~17%) in the risk of heavy drinking relative to the placebo group. Naltrexone-treated patients also showed significant reductions in heavy drinking days, the amount of alcohol consumed, and GGT levels. Naltrexone also decreased drinking days by about 4%, which was not statistically significant.

The vast majority of naltrexone studies have been 3 months or shorter in duration. In a VA multicenter study (Krystal et al., 2001), patients were treated with naltrexone for 12 or 52 weeks. Neither group showed a response that was superior to placebo on any of the outcomes examined. A study of long-acting naltrexone for alcohol dependence (discussed below), which was the basis for its approval by the FDA in 2006, was 6 months in duration (Garbutt et al., 2005).

O'Malley and colleagues (2003) used a primary-care model to treat alcohol-dependent patients initially with open-label naltrexone for 10 weeks, in combination with either cognitive-behavioral therapy (CBT) or a less intensive, supportive approach (primary care management). Although the psychosocial treatment did not moderate the response to medication treatment, patients receiving CBT had a lower risk of drinking. Responders to the initial treatment were then randomly assigned to one of two placebo-controlled, 24-week continuation studies together with either CBT or primary care management. In the primary care management group, naltrexone-treated patients had a higher response rate and lower drinking frequency than those receiving placebo. However, when combined with CBT, naltrexone was no better than placebo. Thus, the initial treatment effects of naltrexone may be maintained using either CBT or a less intensive, supportive treatment together with continued naltrexone administration.

Three main approaches have been employed to enhance the treatment effects of naltrexone in alcohol dependence. These include the use of "targeted" (i.e., as-needed) naltrexone administration in anticipation of high-risk drinking situations (Kranzler et al., 1997, 2003, 2009), long-acting injectable naltrexone formulations (Kranzler et al., 1998, 2004; Garbutt et al., 2005), and genetic moderators of treatment response (Chamorro et al., 2012; Oslin et al., 2003).

TABLE 24.4 Treatment of Alcohol Use Disorder: Meta-analysis of Opioid Antagonists

Authors	*N, Number of Studies*	*Treatment Length*	*Follow-up Length*	*Results*		*Comments*
Rösner et al. (2010b)	7,793 50 studies	4 weeks or longer	Up to 52 weeks	Randomized Controlled Trials		Comprehensive review of studies of alcohol dependence or alcohol abuse; 94% of studies were of naltrexone and 6% were of nalmefene; 88% of studies were two-arm trials; multiple outcome measures evaluated
				Treatment Outcome	Risk Ratio (RR) or Mean Difference (MD) (95% CI)	
	4,433; 28			Return to heavy drinking	RR = 0.83 (0.76, 0.90)	
	4,693; 27			Return to any drinking	RR = 0.96 (0.92, 1.00)	
	3,882; 26			Drinking days	MD = –3.89 (–5.75, –2.04)	
	1,715; 15			Heavy drinking days	MD = –3.25 (–5.51, –0.99)	
	1,838; 16			Consumed per drinking day[a]	MD = –10.83 (–19.69, –1.97)	
	1,645; 16			GGT[b]	MD = –10.37 (–18.99, –1.75)	

[a]In grams of ethanol; [b]Gamma-glutamyltranspeptidase concentration in International Units/L.

Targeted naltrexone may provide an alternative to daily dosing. In an 8-week, placebo-controlled trial of naltrexone 50 mg, 153 problem drinkers were randomly assigned to receive daily medication or medication targeted to situations identified by them as being high risk for heavy drinking (Kranzler et al., 2003). Patients in the targeted condition, irrespective of medication, were less likely to drink. Compared to placebo, naltrexone reduced heavy drinking by 19%. Targeted naltrexone, and to a lesser extent targeted placebo, reduced daily drinking more than daily placebo, an effect that was greater than that of daily naltrexone. A subsequent 12-week comparison of daily or targeted naltrexone with placebo was conducted in 163 problem drinkers whose goal was to reduce their drinking to safe limits (Kranzler et al., 2009). At the end of the study, targeted naltrexone had two significant effects compared to the other three groups: In men, it reduced drinks per day, and in both sexes, it reduced drinks per drinking day.

Heinälä and colleagues (2001) compared naltrexone 50 mg/day with placebo in 121 nonabstinent individuals with alcohol dependence, pairing medication with either coping skills or supportive therapy. During the first 12 weeks of treatment, naltrexone prevented relapse to heavy drinking only in combination with coping skills therapy. During a subsequent 20-week period, during which subjects used their medication in response to alcohol craving, the naltrexone group had a lower rate of relapse to heavy drinking. Together, these findings support the use of targeted naltrexone both in the initial treatment of heavy drinkers and to maintain the beneficial effects of an initial period

of daily naltrexone in alcohol-dependent individuals. This work provided the foundation for the use of as-needed nalmefene, which, as discussed below, is now approved for use in the European Union.

Long-acting, injectable formulations of naltrexone have been developed to enhance adherence with and yield more consistent plasma concentrations of the medication. In a pilot study of 20 alcohol-dependent individuals, treatment with a depot formulation of naltrexone produced by Biotek, Inc. resulted in greater reductions in the frequency of heavy drinking than placebo (Kranzler et al., 1998). Two other long-acting naltrexone formulations have also been tested for safety and efficacy in alcoholics. In a 12-week, placebo-controlled trial in 315 patients who also received motivational enhancement therapy (Kranzler et al., 2004), a long-acting naltrexone formulation produced by DrugAbuse Sciences delayed the onset of any drinking, increased the total number of days of abstinence, and doubled the likelihood of subjects remaining abstinent throughout the study (Kranzler et al., 2004). A third long-acting formulation (Garbutt et al. 2005), produced by Alkermes, was approved by the FDA to treat alcohol dependence based on a study of more than 600 alcohol-dependent patients who were randomly assigned to receive six monthly injections of long-acting naltrexone 380 mg, long-acting naltrexone 190 mg, or matching volumes of placebo. The medication and the injections were well tolerated, with injection site reactions occurring more commonly with the active formulation. Long-acting naltrexone 380 mg resulted in a 25% reduction in the rate of heavy drinking compared to placebo. The long-acting naltrexone 190-mg formulation resulted in a 17% reduction in heavy drinking, which was not significantly better than placebo.

Although there are no head-to-head comparisons of any of the long-acting formulations to oral naltrexone, adherence may be better with the Alkermes formulation than oral naltrexone (Gastfriend, 2011). Six months of treatment with long-acting naltrexone led to significant improvements in measures of quality of life, including those for mental health, social functioning, general health, and physical functioning (Pettinati, Gastfriend, Dong, Kranzler, & O'Malley, 2009). The adverse effects associated with the long-acting naltrexone formulations are similar to those of the oral formulation, including nausea, headache, and fatigue, but long-acting formulations are also associated with local reactions at the injection site.

Pharmacogenetic approaches to naltrexone treatment have focused on a polymorphism in *OPRM1*, the gene encoding the mu-opioid receptor. Carriers of a variant allele (118G or Asp40) may have a better clinical response to naltrexone than individuals homozygous for the more common A118 (or Asn40) allele (Oslin et al., 2003). A recent meta-analysis of the moderating effects of the Asn40Asp polymorphism from six published studies showed that naltrexone-treated patients with one or two copies of the Asp40 allele were more than twice as likely not to relapse to heavy drinking as Asn40-allele homozygotes, with no effect on abstinence rates. Identifying individuals with the Asp40 allele could help to differentiate a subgroup of the population that is more likely to respond to naltrexone treatment. However, the prevalence of the Asp40 allele varies widely by population (>30% in Asians, <20% in individuals of European descent, and <5% in individuals of African descent), so the effects of naltrexone could also vary substantially by population (Arias, Feinn, & Kranzler, 2006).

Nalmefene

In a pilot study (Mason et al., 1994) of nalmefene, also an opioid receptor antagonist, 40 mg/day was superior to 10 mg/day of the drug or placebo in preventing relapse to heavy drinking in a small sample of alcoholics. A subsequent study showed no difference between nalmefene 20 mg/day or 80 mg/day, and when combined, the nalmefene-treated subjects had significantly better outcomes than the placebo group on measures of heavy drinking (Mason et al., 1999). In a 12-week multisite study in recently abstinent outpatient alcoholics, no differences were found between the groups receiving nalmefene (5, 20, or 40 mg/day) versus placebo on drinking outcomes (Anton et al., 2004).

In 2013, based on three multicenter trials of 6 to 12 months in duration, the European Medicines Agency approved nalmefene 18 mg for use on an as-needed basis to reduce heavy drinking in alcohol-dependent individuals. Two of these studies (Gual et al., 2013 Mann et al., 2013) each enrolled more than 600 patients, randomly assigning them to nalmefene or placebo treatment for 6 months. In both studies, nalmefene was statistically superior to placebo in reducing heavy drinking days, with the first study, but not the second one, showing a significantly greater reduction in total alcohol consumption in the

nalmefene group than the placebo group. In the third study (van den Brink et al., 2012), which randomly assigned 665 patients to nalmefene or placebo for a total of 52 weeks of treatment, the medication reduced the number of heavy drinking days and total alcohol consumption beginning in the first month. There was a statistically significant advantage for nalmefene at most time points, including at the end of treatment, but not at the midpoint of the study. Nalmefene also significantly reduced GGT serum concentrations in two of the three studies and alanine aminotransferase serum concentrations in all three studies.

Summary

Although there is evidence supporting the use of naltrexone to treat alcohol dependence, in unselected samples of patients the medication has a small effect size (Rösner et al., 2010b). However, naltrexone may be of particular utility in subgroups of patients. The ready identification of these individuals is of great clinical interest, as is the potential utility of combining naltrexone with other medications and with specific kinds of psychotherapy. New approaches to the use of naltrexone, including targeted administration and long-acting injectable formulations, may enhance its clinical utility. The literature supporting the use of nalmefene includes three large multicenter trials that support its efficacy and have led to its approval in the European Union.

Acamprosate

Acamprosate (calcium acetylhomotaurinate) is an amino acid derivative with weak antagonist effects at NMDA receptors and at a glutamate metabotropic (mGluR5) receptor (Blednov & Harris, 2008; Mann et al., 2008). Based on this, acamprosate may reduce glutamatergic excitability following the cessation of drinking. Initially evaluated in France (Lhuintre et al., 1985), evidence of the medication's efficacy has mostly come from Europe, where some studies have shown persistent beneficial effects of the medication during posttreatment follow-up. Three European studies provided the basis for the approval in 2004 of acamprosate for clinical use in the United States (Paille et al., 1995; Pelc et al., 1997; Sass et al., 1996) (Table 24.5).

A number of meta-analyses have examined the effects of acamprosate (Bouza et al., 2004; Chick,

TABLE 24.5 Treatment of Alcohol Use Disorder: Meta-analysis of Acamprosate

Authors	*N, Number of Studies*	*Treatment Length*	*Follow-up Length*	*Results*		*Comments*
Rösner et al. (2010a)	6,915; 24 studies	4 weeks or longer	12 weeks or longer	Randomized controlled trials		Comprehensive review of studies of alcohol dependence or alcohol abuse; multiple outcome measures evaluated
				Treatment Outcome	Risk Ratio (RR) or Mean Difference (MD) (95% CI)	
	6,172; 24			Return to any drinking	RR = 0.86 (0.81, 0.91)	
	5,224; 19			Cumulative abstinence duration[a]	MD = 10.94 (5.08, 16.81)	
	6 studies			Return to heavy drinking	RR = 0.99 (0.94, 1.04)	
	7 studies			GGT[b]	MD = –11.91 (–24.12, 0.30)	

[a]In days; [b]Gamma-glutamyltranspeptidase concentration in International Units/L

Lehert, Landron, & Plinius Maior Society, 2003; Kranzler & Van Kirk, 2001; Mann, 2004; Rösner et al., 2010a). The most recent meta-analysis included data from 24 RCTs with 6,915 participants. It showed that acamprosate significantly reduced the risk of any drinking and increased the cumulative abstinence duration. The authors concluded that acamprosate appeared to be a safe and effective treatment to support continuous abstinence after detoxification in patients with alcohol dependence, although the size of the treatment effects was modest (Rösner et al., 2010a).

Two large multicenter trials in the United States (Anton et al., 2006; Mason et al., 2006), a large European study (Mann et al., 2009), and an Australian study (Morley et al., 2006) showed no beneficial effects of acamprosate compared with placebo in the treatment of alcohol dependence. In the COMBINE study (Anton et al. 2006), acamprosate did not significantly alter measures of alcohol consumption irrespective of the intensity of the concomitant psychosocial treatment provided, nor did the combination of acamprosate and naltrexone significantly decrease measures of drinking.

The heterogeneity of the samples that are typically enrolled in multicenter studies may have obscured the modest therapeutic effects of the medication. In addition, the substantial difference in the results of published studies could be attributable to the greater severity of alcohol dependence in the studies showing efficacy (i.e., those from Europe).

In summary, meta-analysis of studies enrolling nearly 7,000 patients provides evidence of a beneficial effect of acamprosate in relapse prevention. However, because acamprosate failed to demonstrate efficacy in several large clinical trials, additional research is needed to identify the patient characteristics and therapeutic approaches that contribute to an optimal response to acamprosate.

Anticonvulsants

The potential utility of anticonvulsants to treat alcohol dependence has been shown in placebo-controlled studies of carbamazepine (Mueller et al., 1997), divalproex (Salloum et al., 2005), topiramate (Johnson et al., 2003, 2007; Kranzler et al., 2014), and gabapentin (Anton et al., 2011; Mason et al., 2014). In a 12-month pilot study, Mueller and colleagues (1997) found that carbamazepine reduced drinks per drinking day, time to first heavy drinking day, and consecutive days of heavy drinking more than placebo. Salloum and colleagues (2005) reported that bipolar patients with alcohol dependence treated with valproate had a significantly greater decrease in alcohol consumption than those receiving placebo. Brady and colleagues (2002) found that divalproex was no different than placebo in reducing drinking behavior in a 12-week, double-blind, placebo-controlled pilot study in alcohol-dependent individuals without bipolar disorder.

Anton and colleagues (2011) tested whether the combination of naltrexone 50 mg and gabapentin (up to 1,200 mg/day) was better than naltrexone alone or placebo during the first 6 weeks of a 16-week trial. They found that the combination of gabapentin and naltrexone improved drinking outcomes more than naltrexone alone during the first 6 weeks after the cessation of drinking. The effect did not endure once gabapentin was discontinued.

Subsequently, Mason and colleagues (2014) conducted a 12-week RCT comparing gabapentin 900 mg/day or 1,800 mg/day with placebo and concomitant manual-guided counseling. Gabapentin treatment was associated with higher rates of abstinence and no heavy drinking, evidenced by a linear dose effect. The number needed to treat (NNT) was 8 for the 1,800-mg group. The no-heavy-drinking rate also showed a significant linear dose effect, with the NNT of 5 for the high-dose gabapentin group. Similar effects were seen on measures of mood, sleep, and craving. Interpretation of the study's findings is limited, however, by the low overall rate of study completion (56.7%).

In both single-site and multisite placebo-controlled clinical trials, Johnson and colleagues (2003, 2007) found that topiramate 300 mg/day had a moderate effect in reducing drinks per day, drinks per drinking day, drinking days, heavy drinking days, and GGT concentration. In addition, topiramate treatment decreased compulsive thoughts about drinking, increased psychosocial well-being, and improved the quality of life (Johnson et al., 2008). Although in the single-site study (Johnson et al., 2003) the topiramate and placebo groups were equally likely to complete treatment, in the multicenter study (Johnson et al., 2007) topiramate-treated patients were more likely than placebo-treated patients to discontinue treatment prematurely.

Miranda and colleagues (2008) randomly assigned 61 heavy drinkers to receive treatment with topiramate

200 mg/day, topiramate 300 mg/day, or placebo. They titrated the medication to the target dosage over a 32-day period, maintaining the dosage for 1 week prior to a human laboratory study. During the titration period, the two topiramate groups reduced the frequency of heavy drinking more than placebo, with no significant difference between the two dosages of topiramate. A larger proportion of subjects receiving topiramate 300 mg than topiramate 200 mg or placebo discontinued treatment prematurely.

Recently, a placebo-controlled study conducted in 106 alcohol-dependent patients in Thailand (Likhitsathian et al., 2013) failed to show a significant advantage of topiramate 300 mg/day in reducing drinking. However, in that study, only about half of the patients completed treatment and adherence to the prescribed regimen was not evaluated, factors that limit the interpretation of the results.

In a study of heavy drinkers (the vast majority of whom were alcohol dependent) who wanted to reduce their drinking, participants were randomly assigned to treatment with topiramate 200 mg/day or placebo for 12 weeks (Kranzler et al., 2014). In intent-to-treat analyses, topiramate was significantly better than placebo in decreasing the number of heavy drinking days and increasing the number of abstinent days. Based on prior findings of genetic association to alcohol dependence (Kranzler et al., 2009), rs2832407, a SNP in *GRIK1*, which encodes the GluK1 kainate receptor subunit, was examined as a moderator of topiramate's efficacy in the 128 patients who were of European ancestry. There was a significant interaction of genotype by medication, such that in the CC genotype group but not in the A-allele carrier group, topiramate-treated patients reduced their heavy drinking more than placebo-treated patients.

Topiramate affects multiple neurotransmitter and enzyme systems, so in addition to its effects on drinking behavior, it produces a variety of side effects, the most frequent of which are paresthesia, anorexia and weight loss, difficulty with memory or concentration, and taste disturbances, which are generally mild to moderate in severity. Uncommonly, topiramate causes visual adverse events including myopia, angle-closure glaucoma, and increased intraocular pressure, which require discontinuation of the medication. To minimize topiramate's adverse effects, a slow titration to the maximal dosage is recommended (i.e., over 6 to 8 weeks). Although the optimal topiramate dosage for alcohol treatment has not been determined, the reports by Miranda and colleagues (2008) and Kranzler and colleagues (2014) provide support for the utility of the 200-mg/day dose. Additional research is needed to test the validity of the genetic moderation of topiramate's efficacy in reducing heavy drinking (Kranzler et al., 2014), which has important implications both for the clinical utility of topiramate and for the potential insight that it provides into the mechanism of the medication's effect on heavy drinking.

STIMULANT DEPENDENCE

There are no medications currently approved for the treatment of cocaine or amphetamine/methamphetamine use disorder. However, there are several medications that have shown potential efficacy in controlled clinical trials for cocaine use disorder and a few that have shown potential efficacy for the treatment of methamphetamine use disorder. Medications for the treatment of cocaine use disorder and medications for the treatment of amphetamine/methamphetamine use disorder will be discussed separately (Table 24.6). Only medications that have potential efficacy demonstrated in controlled clinical trials will be presented. Medications for cocaine dependence will be grouped according to the neurotransmitter system they are thought to target. Medications found to be efficacious for cocaine use disorder only when used in conjunction with a novel psychosocial treatment called contingency management will be discussed next. Finally, medications for the treatment of amphetamine/methamphetamine use disorder will be discussed.

Dopamine Agonists for Cocaine Dependence

Agonist treatments have been used successfully to treat both opioid and nicotine use disorders. Ideally, in agonist treatment, the medication chosen should be one that binds to the same receptor as the abused drug, exerts similar effects, and has pharmacological properties that render it less abusable than the abused drug. Methadone, because of its slow onset of action, and buprenorphine, by virtue of its partial agonist activity at the opioid receptors, are effective agonist treatments for opioid use disorder. Likewise, the transdermal nicotine patch's slow absorption contributes

TABLE 24.6 Medications for Cocaine Dependence

Authors	*Class*	*N*	*Treatment Length*	*Follow-up Length*	*Results*	*Comments*
Direct Dopamine Agonists						
Levin at al. (2007)	1	106	14 weeks	—	Cocaine-dependent patients with comorbid attention-deficit/hyperactivity disorder (ADHD). Reduced cocaine use with methylphenidate. No difference in ADHD symptoms.	Methylphenidate was superior to placebo for reducing cocaine use.
Grabowski et al. (2001)	2	128	12 weeks	—	Long-acting dextroamphetamine was superior to placebo in promoting cocaine abstinence in cocaine-dependent patients	High dropout rate
Grabowksi et al. (2004)	2	94	26 weeks	—	Long-acting dextroamphetamine was superior to placebo in promoting cocaine abstinence in cocaine- and opiate-dependent patients maintained on methadone.	High dropout rate
Mooney et al. (2009)	2	82	8 weeks	—	Long-acting methamphetamine was superior to placebo and short-acting methamphetamine in promoting cocaine abstinence in cocaine-dependent patients.	High dropout rate
Mariani et al. (2012)	2	81	12 weeks	—	Mixed amphetamine salts combined with topiramate was superior to placebo in promoting 3 weeks of continuous abstinence from cocaine.	
Other Dopaminergic Medications						
Dackis et al. (2005)	2	62	8 weeks	—	Modafinil superior to placebo in reducing cocaine use	Patients included in this trial did not have comorbid alcohol dependence.
Anderson et al. (2009)	1	210	12 weeks	—	Among cocaine-dependent patients without comorbid alcohol dependence, modafinil was superior to placebo in reducing cocaine use.	Modafinil was not superior to placebo in the overall trial.
Dackis et al. (2012)	1	210	8 weeks	—	Modafinil was not superior to placebo in promoting cocaine abstinence.	

(*continued*)

TABLE 24.6 (continued)

Authors	*Class*	*N*	*Treatment Length*	*Follow-up Length*	*Results*	*Comments*
Carroll et al. (1998)	3	122	12 weeks	—	Disulfiram-treated patients had longer sustained abstinence from cocaine compared to patients treated with psychotherapy alone.	Cocaine-dependent patients with comorbid alcohol dependence were included in this trial.
George et al. (2000)	2	20	12 weeks	—	Disulfiram-treated patients had longer periods of sustained abstinence from cocaine compared to placebo-treated patients.	This was a small pilot trial involving cocaine- and opioid-dependent patients treated with buprenorphine maintenance.
Carroll et al. (2004)	1	121	12 weeks	—	Disulfiram was superior to placebo in reducing the frequency of cocaine use.	Disulfiram was more effective in patients without comorbid alcohol dependence.
Pettinati et al. (2008)	1	208	11 weeks	—	The cocaine-dependent patients with comorbid alcohol dependence treated with the combination of naltrexone and disulfiram were more likely than placebo-treated patients to achieve 3 consecutive weeks of abstinence from both cocaine and alcohol.	Disulfiram, naltrexone, and the combination of the two medications were evaluated in cocaine-dependent patients with comorbid alcohol dependence.
Oliveto et al. (2011)	1	161	14 weeks	—	Disulfiram at 250 mg/day was not better than placebo in reducing cocaine use frequency. Lower doses of disulfiram (62 and 125 mg) were associated with more cocaine use.	Cocaine- and opioid-dependent patients maintained on methadone. Three doses of disulfiram were compared to placebo.
GABAergic/Glutamatergic Medications						
Kampman et al. (2004)	2	40	13 weeks	—	During the last 6 weeks of the trial topiramate-treated patients were significantly more likely to be abstinent from cocaine compared to placebo-treated patients.	Topiramate was tested in a relapse-prevention model in this small pilot trial. Patients had to have low cocaine withdrawal symptoms scores and had at least 3 days of self–reported abstinence before starting topiramate.
Kampman et al. (2013)	1	170	13 weeks	—	Significantly more topiramate-treated patients achieved 3 consecutive weeks of abstinence from cocaine during the last 3 weeks of the trial compared to placebo-treated patients.	Topiramate was tested in a relapse-prevention model. Patients had to achieve a period of abstinence from cocaine long enough to have a cocaine-metabolite-free urine drug screen on the day of randomization.

Johnson et al. (2013)	1	142	12 weeks	—	Topiramate was more efficacious than placebo at increasing the weekly proportion of cocaine nonuse days.	
LaRowe et al. (2013)	1	111	8 weeks	—	Three groups were included in this trial of N-acetylcysteine (NAC) for cocaine dependence: 1200 mg NAC daily, 2400 mg NAC daily, and placebo.	
Medications Combined with Contingency Management (CM)						
Kosten et al. (2003)	1	160	12 weeks	—	The combination of desipramine and CM was associated with more cocaine-metabolite-negative urine drug screens during the trial compared to patients treated with desipramine without CM, placebo with CM, and placebo without CM.	This trial was conducted in patients with comorbid cocaine and opioid dependence being treated with buprenorphine maintenance.
Poling et al. (2006)	1	106	25 weeks	—	Among the 4 groups included in this trial, patients treated with the combination of bupropion and CM had more consecutive weeks of cocaine abstinence compared to the other three groups.	This trial was conducted in patients with comorbid cocaine and opioid dependence being treated with buprenorphine maintenance. There were 4 groups bupropion plus CM, bupropion without CM, placebo with CM, and placebo without CM.
Moeller et al. (2007)	1	76	12 weeks	—	Patients treated with citalopram combined with CM had significantly fewer cocaine-metabolite-positive urine drug screens compared to patients treated with placebo combined with CM.	This was a two-group trial, citalopram and placebo, with both groups receiving CM.
Medications for Methamphetamine Dependence						
Elkashef et al. (2008)	2	151	12 weeks	—	In the group as a whole bupropion was not effective for the treatment of methamphetamine dependence. In a subgroup of light users (18 or less days of methamphetamine use in the 30 days prior to the trial) bupropion-treated patients had significantly more methamphetamine-abstinent weeks compared to placebo-treated patients.	One of two trials in which bupropion showed efficacy in light methamphetamine users

(*continued*)

TABLE 24.6 (continued)

Authors	*Class*	*N*	*Treatment Length*	*Follow-up Length*	*Results*	*Comments*
Shoptaw et al. (2008)	2	73	12 weeks	—	This was a 12-week trial of bupropion for methamphetamine dependence with a 2-week baseline. Urine drug screens were collected three times weekly. In a post hoc analysis, there was a statistically significant effect of bupropion treatment on methamphetamine use among participants with lighter (0–2 positive urine samples) but not heavier (3–6 positive urine samples) use during baseline.	The second trial in which bupropion showed efficacy in light methamphetamine users
Colfax et al. (2011)	2	60	12 weeks	—	This was a trial that involved methamphetamine dependent men who have sex with men. Patients treated with mirtazapine submitted significantly fewer methamphetamine positive urine drug screens during the trial.	This trial was a relatively small pilot. A replication trial has not yet been completed.
Elkashef et al. (2012)	2	140	13 weeks	—	In a small subgroup of patients ($n = 26$) who started the trial with a methamphetamine-negative urine drug screen, topiramate-treated patients had significantly more weeks of abstinence from methamphetamine compared to placebo-treated patients.	In the main trial topiramate was not effective for the treatment of methamphetamine dependence; however, a post hoc analysis showed a relapse-prevention effect for topiramate.

to its effectiveness in the treatment of tobacco use disorder. Cocaine has diverse effects in the brain and, unlike nicotine and opiates, there is not a single molecular target. Therefore, finding an effective agonist treatment for cocaine dependence has been more challenging.

Agonist treatments for cocaine dependence have thus far focused on the dopaminergic properties of cocaine. Early trials with methylphenidate were not positive (Grabowski et al., 1997). However, in at least one trial, Levin and colleagues found that among cocaine-dependent patients with comorbid attention-deficit/hyperactivity disorder, methylphenidate was associated with decreased cocaine use (Levin, Evans, Brooks, & Garawi, 2007).

More success has been achieved with amphetamine and methamphetamine for the treatment of cocaine dependence. In 2001 Grabowski and colleagues published results of the first pilot trial evaluating dextroamphetamine for the treatment of cocaine dependence (Grabowski et al., 2001). In this 12-week trial, 128 cocaine-dependent patients were randomly assigned to placebo, low-dose dextroamphetamine (30 mg/day), or high-dose dextroamphetamine (60 mg/day). Treatment retention was significantly better in the low-dose amphetamine group. Cocaine use was nonsignificantly lower in the high-dose amphetamine group. However, the dropout rate in this study was high. In a subsequent trial by the same group involving 120 cocaine- and opioid-dependent patients stabilized on methadone, significant reductions in cocaine use were seen in patients treated with 60 mg of dextroamphetamine compared to placebo or 30 mg. Again, treatment retention in this trial was poor, with less than 50% of subjects completing (Grabowski et al., 2004). In a trial of immediate- and sustained-release methamphetamine, the sustained-release methamphetamine group submitted significantly fewer cocaine-positive urine drug screens during the trial (29% sustained-release vs. 66% immediate-release vs. 60% placebo). However, this trial too suffered from excessive dropout, with only 32% of the patients completing the trial (Mooney et al., 2009). Although the results in these studies, in general, favored long-acting amphetamine and methamphetamine, the findings in all the trials were difficult to interpret due to high dropout rates.

Modafinil is a medication approved for the treatment of narcolepsy and shift work sleep disorder. It may be useful for the treatment of cocaine-dependent patients through several mechanisms of action, including reductions in cocaine withdrawal symptoms, cocaine craving, or cocaine-induced euphoria. As a mild stimulant, modafinil may be able to reduce cocaine withdrawal symptoms (Dackis & O'Brien, 2003). Modafinil has been shown to increase dopaminergic neurotransmission by blocking the dopamine transporter, and this may account for its ability to reduce cocaine withdrawal symptoms (Volkow et al., 2009). Modafinil also enhances glutamate neurotransmission (Touret et al., 1994). It may therefore be efficacious for cocaine dependence by ameliorating the glutamate depletion seen in chronic cocaine users (Dackis & O'Brien, 2003). Improved baseline glutamatergic tone in the nucleus accumbens prevents reinstatement of cocaine self-administration in an animal model of relapse (Baker et al., 2003).

Modafinil was found to block the euphoric effects of cocaine in three independent human laboratory studies (Dackis et al., 2003; Hart, Haney, Vosburg, Rubin, & Foltin, 2008; Malcolm et al., 2006). First, Dackis and colleagues conducted a double-blind, placebo-controlled cocaine/modafinil interaction trial. In this trial, cocaine-dependent patients were placed on modafinil 200 mg, 400 mg, or placebo and then challenged with 30 mg of intravenous cocaine. Pretreatment with modafinil significantly blunted cocaine-induced euphoria on one of the subjective measures (Dackis et al. 2003). In a separate, but very similar, human laboratory trial, Malcolm and colleagues found that modafinil at both 400 and 800 mg significantly reduced visual analogue scale ratings of "high," "any drug effect," and "worth in dollars" compared to cocaine alone (Malcolm et al., 2006). Finally, Hart and colleagues evaluated the effect of modafinil on the self-administration of cocaine in a human laboratory trial. In this trial, the effects of modafinil maintenance (0, 200, and 400 mg/day) on response to smoked cocaine (0, 12, 25, and 50 mg) were examined in non-treatment-seeking cocaine-dependent individuals (n = 8). Cocaine significantly increased self-administration, subjective-effect ratings, and cardiovascular measures; modafinil at both doses (200 and 400 mg/day) markedly attenuated these effects (Hart et al., 2008).

A double-blind, placebo-controlled pilot trial of modafinil involving 62 cocaine-dependent patients was completed in 2004. In this trial, modafinil-treated patients submitted significantly more

cocaine metabolite-free urine samples compared to placebo-treated patients (42% vs. 22%). Modafinil-treated patients were also rated as more improved compared to placebo-treated patients (Dackis, Kampman, Lynch, Pettinati, & O'Brien, 2005).

The results of the pilot trial were partly replicated in a larger multicenter trial involving 210 cocaine-dependent patients. In this 16-week trial, cocaine-dependent patients were treated with modafinil 200 mg daily, modafinil 400 mg daily, or placebo. In contrast to the pilot trial, in which none of the patients were both cocaine and alcohol dependent, in this trial 41% of the patients were both alcohol and cocaine dependent. In the group as a whole, modafinil was not superior to placebo in promoting abstinence from cocaine. However, among patients who were not also alcohol dependent, both doses of modafinil were superior to placebo for promoting abstinence from cocaine (Anderson et al., 2009). Modafinil may be efficacious only in cocaine-dependent patients without co-occurring alcohol dependence.

Enthusiasm for modafinil is somewhat dampened by results of a clinical trial recently completed by Dackis and colleagues (2012). In this trial, 210 cocaine-dependent patients (without comorbid alcohol dependence) who were actively using cocaine at baseline were randomized to 8 weeks of modafinil (0 mg/day, 200 mg/day, or 400 mg/day) or placebo combined with once-weekly CBT. The investigators found no effect of modafinil at either dose on cocaine use or cocaine craving. Currently there is one more clinical trial of modafinil yet to be completed. At this point, the usefulness of modafinil for the treatment of cocaine dependence has not been definitively established.

Disulfiram may be useful for the treatment of cocaine dependence by a unique mechanism of action. In addition to its effects on alcohol metabolism, disulfiram also blocks the enzymatic degradation of cocaine and dopamine, raising baseline levels of dopamine and causing extremely high cocaine and dopamine levels when cocaine is ingested (Karamanakos, Pappas, Stephanou, & Marselos, 2001; McCance-Katz, Kosten, & Jatlow, 1998). This may affect cocaine use by decreasing the reinforcing properties of cocaine by making cocaine use aversive (Hameedi et al., 1995; McCance-Katz et al., 1998).

In three out of four placebo-controlled clinical trials, disulfiram reduced cocaine use in cocaine-dependent patients (Carroll et al., 2004; Carroll, Nich, Ball, McCance, & Rounsaville, 1998; George et al., 2000; Petrakis et al., 2000). Petrakis and colleagues compared disulfiram to placebo in 67 cocaine- and opioid-dependent patients maintained on methadone. They found that disulfiram-treated patients self-reported significantly less cocaine use in a 12-week trial (Petrakis et al., 2000). In a smaller trial done with cocaine- and opioid-dependent patients maintained on buprenorphine, disulfiram was significantly better than placebo in reducing cocaine use measured by urine drug screens (George et al., 2000). In a trial of 130 cocaine-dependent patients not dependent on opioids, disulfiram was found to be associated with less cocaine use measured by urine drug screens. In this trial patients without a history of alcohol use responded better to disulfiram, confirming disulfiram's specific effect on cocaine use (Carroll et al., 2004). More recently, disulfiram at a dose of 250 mg daily was not found to be superior to placebo in reducing cocaine use in a trial involving 161 cocaine- and opioid-dependent patients maintained on methadone. Moreover, lower doses of disulfiram (62.5 or 125 mg/day) were found to be associated with significantly more cocaine use compared to placebo (Oliveto et al., 2011).

Although Carroll and colleagues (2004) found disulfiram to be more effective in cocaine users without comorbid alcohol dependence, Pettinati and colleagues (2008) found that the combination of disulfiram and naltrexone was better than placebo in promoting sustained abstinence from both cocaine and alcohol in patients with dual cocaine and alcohol dependence. Because of disulfiram's significant cocaine and alcohol interactions, the study of this medication for the treatment of cocaine dependence has largely been abandoned in favor of other dopamine beta-hydroxylase inhibitors without significant cocaine or alcohol interactions, such as nepicastat. Clinical trials with nepicastat have not yet been completed.

GABAergic and Glutamatergic Medications for Cocaine Dependence

Mesocortical dopaminergic neurons receive modulatory inputs from both GABAergic and glutamatergic neurons. GABA is primarily an inhibitory neurotransmitter in the central nervous system. Activation of

GABAergic neurons tends to decrease activation in the dopaminergic reward system. Preclinical trials of medications that foster GABAergic neurotransmission have suggested that these compounds reduce the dopamine response to both cocaine administration and to conditioned reminders of prior cocaine use (Dewey et al., 1992, 1997; Gerasimov et al., 1999). GABAergic medications also reduce the self-administration of cocaine in animal models (Kushner, Dewey, & Kornetsky, 1999; Roberts, Andrews, & Vickers, 1996). Therefore, GABAergic medications could prevent relapse by blocking cocaine-induced euphoria or by reducing craving caused by exposure to conditioned reminders of prior cocaine use. Animal studies of cocaine-induced neuroplasticity have demonstrated that increases in both dopamine and glutamate transmission in the nucleus accumbens are important for the development and expression of the neuroadaptations thought to underlie cocaine addiction (Cornish & Kalivas, 2000). Thus, medications that block glutamatergic input into the nucleus accumbens could reduce cocaine craving and prevent relapse to cocaine use in cocaine-dependent individuals (Kalivas & Volkow, 2011).

Topiramate may be an excellent medication for relapse prevention based on its effects on both GABA neurotransmission and glutamate neurotransmission. Topiramate increases cerebral levels of GABA and facilitates GABA neurotransmission (Kuzniecky et al., 1998; Petroff, Hyder, Mattson, & Rothman, 1999). Topiramate also inhibits glutamate neurotransmission through a blockade of AMPA/kainate receptors (Gibbs, Sombati, DeLorenzo, & Coulter, 2000). In animal models of cocaine relapse, blockade of AMPA receptors in the nucleus accumbens prevented reinstatement of cocaine self-administration (Cornish & Kalivas, 2000).

In a 13-week, double-blind, placebo-controlled pilot trial of topiramate for cocaine dependence involving 40 cocaine-dependent patients, topiramate-treated patients were significantly more likely to be abstinent during the last 5 weeks of the trial compared to placebo-treated patients (Kampman et al., 2004). In addition, among patients who returned for at least one visit after receiving medications, topiramate-treated patients were significantly more likely to achieve at least 3 weeks of continuous abstinence from cocaine compared to placebo-treated patients (59% vs. 26%), and topiramate-treated patients were significantly more likely than placebo-treated patients to be rated very much improved at their last visit (71% vs. 32%) (Kampman et al., 2004).

This pilot trial has now been replicated twice. First, in a 13-week trial that included 170 cocaine- and alcohol-dependent patients, topiramate-treated patients (300 mg/day) were significantly more likely to achieve 3 weeks of continuous abstinence from cocaine at the end of the trial. Twenty percent of the topiramate-treated patients were cocaine abstinent versus 6% of the placebo-treated patients (Kampman et al., 2013). More recently, Johnson and colleagues evaluated the efficacy of topiramate in 142 cocaine-dependent patients in a 12-week double-blind, placebo-controlled trial. In that trial, topiramate-treated patients had significantly more cocaine non-use days than placebo-treated patients during weeks 6 to 12 of the trial. Cocaine non-use days were determined by self-report verified by urine drug screens (Johnson et al., 2013). For the treatment of cocaine dependence topiramate has been found to be efficacious at both 200 mg/day (Kampman et al., 2004) and 300 mg/day (Johnson et al., 2013; Kampman et al., 2013).

Recently, researchers at Columbia conducted a trial of mixed amphetamine salts plus topiramate for the treatment of cocaine dependence. They randomly assigned 81 cocaine-dependent patients to 60 mg of extended-release mixed amphetamine salts plus 300 mg of topiramate daily or identical placebo capsules. They conducted a 12-week trial and found that patients treated with mixed amphetamine salts and topiramate were significantly more likely than placebo-treated patients to achieve 3 weeks of continuous abstinence during the trial (33% vs. 17%) (Mariani et al., 2012). Patients with more baseline cocaine use did the best on this combination. This trial at Columbia took advantage of preliminary findings demonstrating potential efficacy for both long-acting amphetamine and topiramate. The combination of the two medications was effective in this trial. However, whether this positive effect was due to amphetamine, topiramate, or the combination cannot be determined due to the design of this preliminary trial.

Another promising glutamatergic medication is *N*-acetylcysteine (NAC), an amino acid and a cysteine pro-drug. Preclinical and some early pilot clinical trials have suggested that it may be an effective medication for the treatment of addictive disorders. Preclinical studies have suggested that

levels of glutamate in the nucleus accumbens mediate reward-seeking behavior (Kalivas & Volkow, 2005; McFarland, Lapish, & Kalivas, 2003). Low levels of extracellular glutamate in the nucleus accumbens are associated with chronic cocaine exposure. Through stimulation of the cysteine-glutamate antiporters, NAC may increase extracellular glutamate levels. This in turn modulates the release of glutamate in response to drug taking via stimulation of metabotropic glutamate autoreceptors. This reduction in glutamate release may block drug-seeking behaviors and drug craving. In rats, NAC pretreatment blocked the reinstatement of drug-seeking behavior induced by cocaine or conditioned cues of cocaine (Baker et al., 2003). In a human laboratory trial, NAC reduced cocaine craving in non-treatment-seeking cocaine-dependent men and women (LaRowe et al., 2007). In an open-label trial, NAC was found to be safe and well tolerated in cocaine-dependent patients (LaRowe et al., 2006). Most recently, NAC was found to be superior to placebo in preventing relapse in cocaine-dependent patients. This trial involved 111 cocaine-dependent patients treated with NAC 1,200 mg, NAC 2,400 mg, or placebo for 8 weeks. Among patients who had achieved abstinence prior to starting NAC, those treated with 2,400 mg/day had a significantly longer time to relapse compared to placebo-treated patients (LaRowe et al., 2013).

Combining Contingency Management with Medications

Voucher-based reinforcement therapy (VBRT) is a behavioral treatment intervention for SUDs in which patients receive vouchers redeemable for goods and services in the community contingent upon achieving a predetermined therapeutic goal. VBRT targeting cocaine abstinence has been shown to be highly effective in promoting initial abstinence from cocaine among cocaine-dependent patients (Higgins et al., 1994). Researchers have begun to combine VBRT with medications to augment medication response in cocaine-dependent patients. In several trials, patients treated with the combination of VBRT targeting abstinence and medications have responded better than patients treated with either medications or VBRT alone. For example, Kosten and colleagues tested the efficacy of desipramine and VBRT in cocaine- and opiate-dependent patients maintained on buprenorphine. Desipramine had been studied for the treatment of cocaine dependence in the 1980s, but in association with standard psychosocial treatment it was not found to be consistently efficacious. In this trial, patients received desipramine or placebo with VBRT or a noncontingent voucher control. Cocaine-free and combined cocaine- and opiate-free urine samples increased more rapidly over time in those treated with desipramine or VBRT. Those receiving both VBRT and desipramine had significantly more drug-free urine samples than the other three groups (Kosten et al., 2003).

In a double-blind, placebo-controlled trial of bupropion and VBRT, the combination of bupropion and VBRT was found to be superior to bupropion alone, placebo bupropion, and VBRT alone in promoting abstinence from cocaine in cocaine-dependent patients (Poling et al., 2006). Similar results were found for the combination of the SRI citalopram and VBRT (Moeller et al., 2007). Several SRIs have been tested for the treatment of cocaine dependence but, like desipramine, SRIs have not been found to be consistently efficacious when used in association with standard psychosocial treatment. The use of VBRT targeting cocaine abstinence as a psychosocial treatment platform appears to be effective in increasing the efficacy of certain medications for the treatment of cocaine dependence.

Medications for Amphetamine Dependence

The effort to find medications for the treatment of amphetamine and methamphetamine use disorders started more recently than the search for a medication to treat cocaine dependence. Consequently, fewer medications have been tested. Similarities between the mechanisms of action of these drugs have suggested that medications effective for cocaine dependence may also be effective for amphetamine and methamphetamine dependence, and several medications being tested for cocaine dependence are currently undergoing or are about to undergo testing for methamphetamine dependence. So far only bupropion, topiramate, and mirtazapine have shown evidence of potential efficacy in controlled clinical trials.

Bupropion is an antidepressant medication that acts primarily as a reuptake inhibitor of dopamine and norepinephrine. It has also been shown to be

effective for the treatment of nicotine dependence. Bupropion may be effective for smoking and methamphetamine dependence by virtue of its effects on dopamine reuptake. Bupropion was thought to potentially alleviate stimulant withdrawal symptoms by facilitating dopamine neurotransmission. Bupropion was tested for cocaine dependence in the past and found to be ineffective (Margolin et al., 1995). For methamphetamine dependence, bupropion has been shown to be more promising.

Bupropion was tested for the treatment of methamphetamine dependence in 151 methamphetamine-dependent patients. In the group as a whole, there was a nonsignificant trend toward more weeks of abstinence from methamphetamine in the bupropion condition compared to placebo. In a subgroup of patients with less methamphetamine use at baseline, bupropion treatment was associated with significantly more weeks of abstinence from methamphetamine compared to placebo treatment (Elkashef et al., 2008). This finding was replicated in a subsequent trial involving 73 methamphetamine-dependent outpatients. Among light methamphetamine users (defined as zero to two out of six amphetamine-positive urine samples during a 2-week baseline), bupropion-treated patients compared to placebo-treated patients had significantly more methamphetamine-free weeks measured by negative urine drug screens (Shoptaw et al., 2008). Hence, for less severe amphetamine users, bupropion may be efficacious.

Preliminary evidence suggests possible efficacy for two more medications, topiramate and mirtazapine. Topiramate was tested for the treatment of methamphetamine dependence in a single study, a 13-week multicenter trial involving 140 methamphetamine-dependent patients who were randomly assigned to either topiramate 200 mg daily or identical placebo capsules. In the intent-to-treat analysis, topiramate did not increase abstinence from methamphetamine during the target weeks 6 to 12. However, topiramate reduced weekly median urine methamphetamine levels and observer-rated severity of dependence scores significantly. Subjects with negative urine screens before randomization had significantly greater abstinence if treated with topiramate versus placebo during study weeks 6 to 12 (Elkashef et al., 2012). Topiramate was safe and well tolerated in this trial.

The antidepressant mirtazapine is another medication with some positive preliminary data for the treatment of methamphetamine dependence. Mirtazapine blocks alpha 2-autoreceptors and alpha 2-heteroreceptors as well as 5-HT2 and 5-HT3 receptors. It is thought to raise synaptic levels of serotonin, norepinephrine and dopamine. Mirtazapine was evaluated in 60 methamphetamine-dependent men who have sex with men in a 12-week double-blind, placebo-controlled trial. Patients treated with mirtazapine submitted significantly fewer methamphetamine-positive urine drug samples during the trial (Colfax et al., 2011).

Conclusions

The goal of finding a medication FDA approved for the treatment of cocaine or amphetamine/methamphetamine dependence has not been achieved. Nevertheless, several medications for the treatment of cocaine dependence have shown promise in controlled trials and continue to be studied. Dopamine agonists and topiramate appear to be most promising at this point. For the treatment of amphetamine dependence, many more preliminary trials will need to be done because the process of medication development for this illness is not as far along. Preliminary results have shown a consistent response for bupropion for amphetamine-dependent patients with less severe disease and some early positive responses with topiramate and bupropion.

OPIOID DEPENDENCE

Although the history of opiate addiction in the United States goes back more than 100 years, most of the societal response has been legal rather than medical. Physicians are heavily restricted in their ability to deal with opiate addiction as a medical problem. Most treatment consists only of detoxification—that is, removal of the drug from the body by metabolism while withdrawal symptoms are being treated by another medication. In reality, detoxification is simply a first step in a long-term relapse-prevention program. Two medical approaches to aid in detoxification are available. One is the use of an opioid agonist in gradually decreasing doses over 5 to 10 days. This permits a smooth, comfortable detoxification for most patients. A long-acting medication such as methadone or buprenorphine is preferable because

it permits a smooth transition to the drug-free state. A second option is the use of a drug that blocks certain aspects of the withdrawal syndrome, such as clonidine or lofexidine.

Methadone

Some opioid addicts are able to detoxify and remain drug-free, but the majority relapse, even after intensive psychotherapy. More important, many heroin addicts will not even consider a drug-free treatment approach or entry into a therapeutic community. Maintenance treatment using methadone (Table 24.7), which was developed in the 1960s, consists of transferring the patient from heroin, a short-acting opiate that must be taken by injection two to four times daily, to methadone, a long-acting opioid that need be taken only once daily by mouth. The changes produced by transfer to a long-acting opioid are significant. The treatment requires relatively little effort on the part of the patient, giving it wide appeal. This appeal is important from a public health perspective because infections such as HIV and resistant tuberculosis threaten the general public as well as substance abusers.

Initially, most heroin addicts have poor motivation to change their lives. When first introduced to methadone treatment, they still want to get "high" and mix other drugs with prescribed medication. With appropriate counseling in a structured program, the patient can make the transition from thinking like a street addict to being a productive citizen. Methadone substitutes for heroin, reduces drug-seeking behavior, and blocks opiate withdrawal symptoms. It stabilizes physiological systems because of its long duration of action in contrast to the short action of heroin, which produces ups and downs (Kreek, 1992). Typically patients continue to use some heroin during the first few weeks or months on methadone. Methadone does not block the effects of heroin, but it produces cross-tolerance to heroin and all similar drugs. Thus, the effects of usual doses of heroin are diminished, and over time the typical patient decreases heroin use further and then stops.

Randomized studies have strongly supported the efficacy of methadone when used as a maintenance medication. A recent Cochrane Collaboration review (Mattick, Breen, Kimber, & Davoli, 2009) that included 11 studies compared methadone maintenance to no-opioid-replacement control groups (e.g., placebo medication, offer of drug-free treatment, detoxification, or waitlist control). The results indicated that methadone maintenance produced significantly longer retention in treatment (older studies RR = 3.05, 95% CI: 1.75–5.35; newer studies RR = 4.44, 95% CI: 3.26–6.04) and lower rates of opiate use as indicated by self-reported heroin use and biological measures (urine toxicology or hair analysis) (RR = 0.66, 95% CI: 0.56–0.78), compared to the control conditions. Methadone maintenance was also associated with less criminal activity (RR = 0.39, 95% CI: 0.12–1.25) and lower mortality rates (RR = 0.48, 95% CI: 0.10–2.39), although these findings were not statistically significant due to a smaller number of studies that considered these outcomes.

A comprehensive review of prior systematic reviews and more recent studies not included in these reviews also strongly supported the clinical effectiveness of methadone maintenance versus no drug therapy or placebo (Connock et al., 2007). This review indicated that methadone produced longer retention (pooled RR = 3.91, 95% CI: 1.17–13.2) and lower rates of opiate use (pooled effect size = 0.65, 95% CI: 0.41–0.89).

There is also some evidence that indicates the improvements shown by methadone patients are produced by a combination of medication (methadone) and psychosocial intervention (Connock et al., 2007). When methadone dose is held constant at a level adequate for most patients (60 mg), there is an orderly relationship between the "dose" of psychotherapy and the outcome of treatment (McLellan et al., 1993). Some improvement is seen with methadone alone, but with increments in psychosocial interventions, there is significantly greater improvement as measured by illicit drug use, psychiatric symptoms, family problems, and employment. Other studies have demonstrated that patients on methadone become healthier and have lower rates of exposure to infections, including HIV (Metzger et al., 1993).

The physiological stability produced by methadone is demonstrated in several ways. Patients report fewer sleep problems and less depression. Women report irregular menses while on heroin, but on methadone there is at first a suppression of menstruation and then, after about 6 to 12 months, a resumption of regular cycling. A similar stabilization is noted in the hypothalamic-pituitary-adrenal axis. Women can conceive while on methadone, and the babies are born physically dependent on the opioid. While on

TABLE 24.7 Medications for Heroin Dependence: Methadone

Authors	*Study Class*	*N, Number of Studies*	*Treatment Length*	*Follow-up Length*	*Results*		*Comments*
Mattick et al. (2009)	4	11 studies	1 month or longer	1 month or longer			Cochrane Collaboration Review.
					Outcome	Risk Ratio (95% CI)	
		505; 3			Retention, older studies	3.05 (1.75–5.35)	
		750; 4			Retention, newer studies	4.44 (3.26–6.04)	
		1129; 6			Opiate use: urine or hair analysis	0.66 (0.56–0.78)	
		363; 3			Criminal activity	0.39 (0.12–1.25)	
		576; 4			Mortality	0.48 (0.10–2.39)	
Connock et al. (2007)		31 reviews and 28 RCTs					Comprehensive review of prior systematic reviews and newer RCTs
					Retention	3.91 (1.17–13.20)	
					Opiate use	0.65 (0.41–0.89)	

methadone, expectant mothers can receive good prenatal care, and the withdrawal syndrome in newborns is readily treated. Although it would be preferable to have women drug-free during pregnancy, babies born to methadone-treated mothers are significantly healthier than babies born of mothers using street heroin.

Brief maintenance (extended detoxification) as defined by federal methadone regulations is up to 180 days of methadone treatment. This is enough time to give some patients a stable period during which they can organize their lives and become engaged in psychotherapy. Six months is too short for most patients, however, and the duration of methadone treatment should be determined by the patient's needs and not by an arbitrary time limit. Some patients require several years of stable methadone maintenance before they can be gradually detoxified by decreasing the dose of methadone. Many others require indefinite maintenance on this medication. For these patients, methadone should be considered as a kind of "hormone replacement therapy" analogous to thyroxine for patients with hypothyroidism or prednisone for patients with Addison's disease.

The endogenous opioid system is so complicated that a simple diagnostic test has not yet been devised that could demonstrate a primary or secondary deficiency state, if one existed. Some data measuring spinal fluid or plasma endogenous opioids from addicts do exist, but they are limited to individual peptides and do not give a clear picture of the overall system (O'Brien, 1993). There are also data from nonaddict populations showing that the system can

be congenitally hyperactive, resulting in babies born with stupor and respiratory depression that is reversed by opiate antagonists such as naloxone or naltrexone (Myer, Morris, Brase, Dewey, & Zimmerman, 1990). It is theoretically possible, therefore, that other individuals could be born with congenitally low endogenous opioids, possibly giving them a lower threshold for pain and making them more vulnerable to becoming opioid addicts. It is also possible, but not clearly demonstrated, that years of taking exogenous opiates, such as heroin, could suppress the production of endogenous opioids and create a need for lifetime methadone as "hormone replacement." This would explain why many former opioid addicts are unable to remain free of exogenous opioids despite apparently good motivation.

A hypothetical derangement of the endogenous opioid system would also be consistent with data demonstrating a protracted opioid withdrawal syndrome (Martin & Jasinski, 1969). Although the acute opioid withdrawal syndrome diminishes in a matter of 5 to 10 days whether or not treatment is received, a more subtle withdrawal syndrome lasting 6 months has been described under controlled inpatient conditions. Symptoms consist of sleep disturbance and dysphoria with accompanying disturbances in appetite, blood pressure, and cortisol rhythms. These symptoms would be expected to increase the probability of heroin use if the patient were in an environment where opiates were available.

Despite overwhelming evidence demonstrating efficacy (see Table 24.7), methadone remains a controversial treatment (Institute of Medicine, 1990). Methadone produces clear functional improvement, but not a cure. The patient remains physically dependent on a synthetic replacement medication and is capable of functioning normally. Tolerance develops to the sedating effects of opioids, and patients receiving methadone are quite alert (Zacny, 1995) and capable of operating motor vehicles and performing complex tasks such as teaching school or practicing law or medicine. Unfortunately, methadone programs are generally underfunded, and some programs do little more than dispense methadone. This can be of some benefit, but the full impact of methadone treatment requires a structured counseling/psychotherapy program. Eventually, frequent counseling sessions become unnecessary, and patients can be trusted to take methadone at home. Legal requirements permit only limited doses to be prescribed for use at home, even for patients who have demonstrated their trustworthiness.

Buprenorphine

Buprenorphine (Table 24.8) belongs to another class of medications called *partial agonists*. It was originally approved for the treatment of pain but has also shown good efficacy as a maintenance drug in clinical trials among heroin addicts. As a partial mu opiate agonist, buprenorphine activates opiate receptors, producing effects similar to those of heroin and methadone, but there is a "ceiling" such that higher doses produce no greater effect. In studies so far, overdose from buprenorphine alone has occurred rarely, if at all, but the drug can be lethal when mixed with benzodiazepines in high doses. If heroin or other opioids are taken, their effects are attenuated or blocked by the presence of buprenorphine. Buprenorphine

TABLE 24.8 Medications for Heroin Dependence: Buprenorphine

Authors	*Study Class*	*N, Number of Studies*	*Dose*	*Follow-up Length*	*Results*		*Comments*
					Outcome	Risk Ratio or SMD (95% CI)	
Mattick et al. (2008)	4	1131; 5	Low		Retention	1.50 (1.19–1.88)	
		887; 4	Medium		Retention	1.74 (1.06–2.87)	
		728; 4	High		Retention	1.74 (1.02–2.96)	
		487; 2	Low		Opioid use—urinalysis	0.10 (–0.80–1.01)	
		463; 2	Medium		Opioid use—urinalysis	–0.28 (–0.47–0.10)	
		620; 3	High		Opioid use—urinalysis	–1.23 (–0.95 to –0.51)	

was approved for treatment of opiate addiction in the United States in 2002. A unique aspect is that it can be prescribed in a doctor's office, thus eliminating the need to attend a strictly controlled methadone clinic.

Buprenorphine for the treatment of opioid dependence is available in two forms. The most commonly used form is buprenorphine combined with naloxone in a ratio of 4 to 1 (buprenorphine to naloxone). The combination product is intended to discourage intravenous abuse of buprenorphine. Naloxone has poor sublingual bioavailability. When the combination product is used sublingually, the effect is that of buprenorphine. If the product is diverted and used intravenously, the predominant effect is that of naloxone, which does not result in opioid high and may result in precipitated withdrawal in individuals physically dependent on opioids. The use of buprenorphine alone (without naloxone) should be reserved for pregnant women. The effects of naloxone on the developing fetus are unknown.

To legally prescribe buprenorphine, physicians must take a formal course on the drug to obtain a special license, and they are limited to 30 patients on this medication at any one time in their first year of practice, and 100 patients thereafter. The results of clinical trials are roughly similar to those involving methadone, although heroin addicts with a high degree of physical dependence may require the full agonist benefits of methadone (R. E. Johnson et al., 2000). The upper limit of buprenorphine effects is equivalent to about 40 mg of methadone. Based on experience from clinical trials, some heroin addicts prefer methadone, and others state that they feel the most stable and alert on buprenorphine. As with the treatment of other diseases, it is helpful for the clinician to have a selection of medications from which to choose.

A meta-analysis of studies that have compared buprenorphine maintenance to placebo was conducted recently by the Cochrane Collaborative (Mattick, Kimber, Breen, & Davoli, 2008). This review examined retention and opiate (urine toxicology), cocaine, and benzodiazepine use outcomes. The analyses broke studies down by the dose of buprenorphine that was provided. Low (RR = 1.50, 95% CI: 1.19–1.88), medium (RR = 1.74, 95% CI: 1.06–2.87), and high (RR = 1. 74, 95% CI: 1.02–2.87) doses of buprenorphine produced better retention rates than placebo. Medium (std. mean difference = –0.28, 95% CI: –0.47–0.10) and high doses (std. mean difference = –1.23, 95% CI: –0.95 to –0.51) of buprenorphine produced lower rates of heroin use than placebo, but low-dose buprenorphine did not differ from placebo (std. mean difference = 0.10, 95% CI: –0.80–1.01). Buprenorphine was generally not efficacious with regard to cocaine or benzodiazepine use.

Several other studies have investigated strategies to improve outcomes in buprenorphine treatment. One study tested whether increasing dosing in standard primary care medical management from one to three times per week and providing additional drug counseling in the sessions improved outcomes (Fiellin et al., 2006). Results indicated no advantage to more frequent dosing or additional drug counseling on drug use or retention. Combining naltrexone with buprenorphine produced better retention and drug use outcomes than buprenorphine only in another randomized study, as well as better scores on measures of irritability, depression, tiredness, and craving (Gerra, Fantoma, & Zaimovic, 2006). Kakko and colleagues (2007) found that a stepped-care protocol, in which patients began on buprenorphine and escalated to methadone if they did not do well on buprenorphine, produced retention and drug use outcomes that did not differ from a group randomized to initiate treatment on methadone. About half the participants (46%) in the stepped-care condition were able to remain on buprenorphine, which is a safer medication.

A two-phase adaptive trial by Weiss and colleagues (2011) with patients dependent on prescription opioids found that brief treatment (4 weeks) with buprenorphine–naloxone produced very poor outcomes (6.6% positive response rate), even when more intensive counseling was added. Providing nonresponders with 12 more weeks of buprenorphine–naloxone increased the positive response rate to 49.2%, but the rate dropped to 8.6% at 8 weeks after medication had been discontinued. Once again, there was no effect for more intensive counseling. In a second trial, investigators evaluated the efficacy of a brief stabilization with buprenorphine followed by oral naltrexone treatment. In this trial 50% of patients treated with a 4-week buprenorphine stabilization followed by 6 weeks of oral naltrexone therapy were abstinent from opioids at their last study visit (Sigmon et al., 2013). The results of these two trials suggest that buprenorphine can be effective for the treatment of prescription opioid dependence but brief treatments are likely to be ineffective.

Finally, Ling and colleagues (2010) tested the efficacy of buprenorphine implants, which address the problems with adherence and diversion that have been noted in clinical practice and research studies. Opioid-dependent patients randomized to buprenorphine implants had a higher percentage of opiate-negative urine samples over the 16-week trial than those who received a placebo implant (40.4% vs. 28.3%, $p = 0.04$). These results were obtained even though patients in both conditions could receive buprenorphine–naloxone tablets for emergent withdrawal or craving, and 91% of those in the placebo condition received these tablets, for an average of 19 days.

Methadone Versus Buprenorphine Maintenance

A meta-analysis of studies that have compared methadone maintenance and buprenorphine maintenance was conducted recently by the Cochrane Collaborative (Mattick, Kimber, Breen, & Davoli, 2008). This review examined retention, opiate use (biological assays and self-report), cocaine use, benzodiazepine use, and criminal activity. The analyses broke studies down by the dose of methadone and buprenorphine that were provided. Buprenorphine had lower retention rates than methadone in studies with flexible doses (RR = 0.85, 95% CI: 0.73–0.98) and those with low doses (RR = 0.67, 95% CI: 0.52–0.87), but not in studies with medium doses.

There was little evidence of any differences between methadone and buprenorphine maintenance on opioid urine toxicology or self-report outcomes, with the exception of opioid urine toxicology results favoring methadone when medium doses of both drugs were used (std. mean difference = 0.27, 95% CI: 0.05–0.50). There were no differences between the two medications on cocaine use, benzodiazepine use, or criminal activity. However, a second systematic review found that at equivalent doses methadone maintenance was more effective than buprenorphine maintenance on cocaine abstinence in patients with comorbid opioid and cocaine dependence (RR = 1.63, 95% CI 1.20–2.22, $p = 0.002$) (Castells, Kosten, Capella, Vidal, Colom, & Casas, 2009).

Opioid Antagonist Treatment

The discovery of specific opiate receptor antagonists in the early 1970s gave rise to hopes for the "perfect" medication for the treatment of heroin addiction. Naltrexone (Table 24.9) seemed to be the answer because it specifically blocks mu opiate receptors and, to a lesser extent, kappa receptors and delta receptors (Raynor et al., 1994), and it has little or no direct or agonist effects of its own. Naltrexone and its short-acting analogue naloxone have high affinity for opiate receptors and will displace drugs like morphine or methadone, resulting in the sudden onset of withdrawal symptoms when given to people who are opioid dependent. If the heroin addict is first detoxified so that opiate receptors are gradually evacuated, naltrexone will bind to the receptors and prevent subsequent injections of heroin from having an effect. Numerous clinical trials showed that naltrexone was effective in blocking opiate receptors and safe; thus, it was approved by the FDA in 1983 for maintenance treatment of heroin addiction.

Unfortunately, naltrexone is a much-underused medication in the treatment of heroin addiction. Unlike methadone, it has no positive psychoactive effects. Few street heroin addicts show any interest in this type of treatment, and few programs encourage patients to try it. Opioid antagonists are more complicated to prescribe than methadone, and most physicians have not been trained in their use. Opioid-dependent health care workers such as physicians, pharmacists, and nurses often do well on naltrexone because it enables them to return to work with no risk of relapse even though they work in areas with high drug availability. There is also evidence that naltrexone is helpful in preventing relapse in probationers who have a conditional release from prison after drug-related crimes (Brahen, Henderson, Copone, & Kordal, 1984; Cornish et al., 1997).

A recent multisite study done in Russia randomly assigned 250 opioid-dependent patients to placebo or an injectable form of naltrexone, both of which were administered by monthly injections for 6 months. All patients also were offered behavioral treatment, in the form of biweekly drug counseling sessions. Injectable naltrexone produced a higher percentage of urine-test-confirmed abstinent weeks (90.0% vs. 35.0%, $p = 0.0002$) and a higher percentage of patients with confirmed abstinence over the whole trial (45% vs. 28%, $p = 0.02$) than placebo.

Experience with naltrexone demonstrates that blocking opiate receptors does not impair normal function for most people. Studies in animals have implicated opiate receptors in a wide variety of functions

TABLE 24.9 Medications for Heroin Dependence: Naltrexone

Authors	*Study Class*	*N*	*Treatment Length*	*Follow-up Length*	*Results*	*Comments*
Lerner et al. (1992)	1	31	–	2 months	Craving reduced in naltrexone group; reports of euphoria blocked when opiates used, but no evidence of reduced drug use as compared with placebo	–
Shufman et al. (1994)	2	32	3 months	–	Fewer heroin-positive urine tests, more drug-free patients, more improvement in psychological parameters in naltrexone group	Small sample size.
Gerra et al. (1995)	1	152	3 months	6 months	Double-blind, placebo-controlled 3 months of daily medication: clonidine only, clonidine and naltrexone, clonidine and naloxone; placebos. Better results with longer duration of naltrexone treatment.	Consistent with prior studies showing high dropout rate, but good results for patients who remain longer
Cornish et al. (1997)	1	51	6 months	6 months	All participants were volunteers from federal probation. Those randomized to control group received equivalent counseling, but no placebo. 52% completion in naltrexone vs. 33% for controls. Opioid use 8% in naltrexone vs. 30% for controls. Only 26% of naltrexone groups were reincarcerated vs. 56% for controls.	Demonstrates potential usefulness of naltrexone in a parole population
Comer et al. (2006)	1	60	2 months	–	Depot naltrexone, Biotek version, placebo, 192 or 384 mg depot naltrexone per month; treatment retention, dose-related, 39%, 60%, 69% retention, positive urine samples varied according to dose	Minimal side effects.
Krupsky et al. (2011)	1	250	6 months	–	Opiate-dependent patients with 7 or more days of opiate abstinence were randomized to 380 mg extended-release naltrexone (XR-NTX) or placebo. Median proportion of weeks of confirmed abstinence was 90.0 in XR-NTX group, compared to 35.0 in the placebo group ($p = 0.0002$). Results with retention and secondary substance use outcomes also were significantly better in the XR-NTX condition.	XR-NTX is injectable, extended-release naltrexone. Injections provided every month

such as control of appetite, sexual behavior, and, of course, pain perception. Occasionally, normal volunteers given naltrexone report dysphoria or depression, but most former heroin addicts have few symptoms related to the antagonist. Some have remained on naltrexone for up to 20 years with no apparent change in appetite or pain perception and no impairment of ability to experience pleasure from sources such as sex or music. The recent approval of depot naltrexone should have an immediate positive effect on the treatment of heroin addiction. Although the cost of monthly injections will likely be an issue, it will be far less than the costs of drug-related crime and imprisonment.

CONCLUSIONS

The studies reviewed in this chapter indicate that, at this time, there are medications with at least some degree of efficacy in the treatment of nicotine, alcohol, and opiate use disorders. Several medications approved for other indications have shown efficacy for cocaine addiction. Methamphetamine addiction is the target of intense clinical research at present, and a medication that aids in the treatment of this difficult addiction will likely be discovered in the future. In addition, medications aimed at the treatment of drug craving are beginning to appear (O'Brien, 2005). Long-term psychosocial interventions should generally be used in conjunction with pharmacotherapy when treating SUDs to facilitate retention and compliance and to address the myriad of psychological and social problems that often accompany addiction (O'Brien, 1996). It is also important to treat comorbid psychiatric disorders, particularly when they are either preexisting or independent of the SUD. Additional studies are needed to examine issues such as the long-term efficacy and effectiveness of existing and new medications, matching subgroups of patients to particular medications, and potential dangers associated with severe relapse while on medications (Schuckit, 1996).

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25

Treatments for Gambling Disorder and Impulse Control Disorders

Jon E. Grant
Brian L. Odlaug
Marc N. Potenza

Several controlled outcome studies (type 1 and type 2) suggest that specific behavioral (e.g., cognitive-behavioral therapy [CBT]) and pharmacological (e.g., naltrexone, nalmefene, lithium) treatments significantly reduce the symptoms of pathological gambling (now termed gambling disorder in *DSM-5*) in the short term compared with waitlist or placebo. Although long-term effects of manual-based CBT have been observed in several small studies, the long-term benefits of pharmacological treatment have not been adequately tested. Only one study combining behavioral and pharmacological therapies has been published to date. Thus, the potential benefit of combining behavioral and drug treatments for gambling disorder remains underresearched. Although several studies suggest that CBT is effective for trichotillomania, only two pharmacological treatment studies (both type 1) in adults (*N*-acetylcysteine [NAC], olanzapine) for this disorder have shown promise. Similarly, studies of group CBT (type 1) have demonstrated benefit for compulsive buying, but controlled pharmacological studies (type 1 and type 2) have shown mixed results. Although limited treatment studies exist for other impulse control disorders, one pharmacological study for kleptomania (type 1) and one for intermittent explosive disorder (IED type 1) have shown promise.

INTRODUCTION

Despite high prevalence rates in the general population (Kessler et al., 2005) and in psychiatric cohorts (Grant, Levine, Kim, & Potenza, 2005), impulse control disorders have been relatively understudied. Controlled treatment trials do not exist for many of the impulse control disorders. The disorder that has been arguably the most well researched (pathological gambling, which is now gambling disorder [GD] in *DSM-5*; we will use the term *GD* throughout the chapter to refer to pathological gambling or GD) has only recently been systematically investigated with respect to empirically supported behavioral and pharmacological treatments. Because rigorous research is particularly limited for several impulse control disorders (e.g., pyromania and Internet gaming disorder), this chapter reviews the available research on the treatment of gambling disorder, trichotillomania, compulsive buying, IED, and kleptomania.

Although this chapter reviews the pharmacological and psychological treatment of GD along with that of impulse control disorders, GD is now part of a new *DSM-5* section entitled "substance-related and addictive disorders." The similarities between GD and substance use disorders (e.g., phenomenology/clinical presentation, comorbidity, familiality, cognition, neuroanatomy/neurochemistry, and treatment) led to this

reclassification of GD together with substance use disorders in *DSM-5* (Grant & Chamberlain, 2013).

GAMBLING DISORDER

GD, characterized by persistent and recurrent maladaptive patterns of gambling behavior, is associated with impaired functioning, reduced quality of life, and high rates of bankruptcy, divorce, and incarceration (Hodgins, Stea, & Grant, 2011). GD usually begins in adolescence or early adulthood, with males tending to start at an earlier age (Ibanez, Blanco, Moreryra, & Saiz-Ruiz, 2003; Shaffer, Hall, & Vander Bilt, 1999). In epidemiological studies, women represent approximately 32% of individuals with GD in the United States (Volberg, 1994). Although prospective studies are largely lacking, GD appears to follow a similar trajectory as substance dependence, with high rates in adolescent and young adult groups, lower rates in older adults, and periods of abstinence and relapse (Grant & Potenza, 2004; Leeman & Potenza, 2012).

Males with GD appear more likely to report problems with strategic or "face-to-face" forms of gambling like blackjack or poker. Females with GD tend to report problems with nonstrategic, less interpersonally interactive forms of gambling like slot machines or bingo (Potenza et al., 2001). Both female and male gamblers report that advertisements are common triggers for their urges to gamble, although females are more likely to report that feeling bored or lonely may also trigger their urges to gamble (Afifi, Cox, Martens, Sareen, & Enns, 2010; Echeburúa, González-Ortega, de Corral, & Polo-López, 2011). Financial and marital problems are common (Grant & Kim, 2001). Many individuals with GD engage in illegal behavior, such as stealing, embezzlement, and writing bad checks, to fund their gambling (Potenza et al., 2000). GD frequently co-occurs with other psychiatric disorders, including mood, anxiety, and substance use disorders (Lorains, Cowlishaw, & Thomas, 2011; Petry, Stinson, & Grant, 2005) and is associated with poor overall health (Morasco, Vom Eigen, & Petry, 2006; Pietrzak, Morasco, Blanco, Grant, & Petry, 2007).

Pharmacological Treatment

Several medications have been investigated as treatments for GD (Table 25.1). These have included antidepressants (particularly serotonin reuptake inhibitors [SRIs]), lithium, glutamate agents, neuroleptics, and opioid antagonists. Multiple open-label studies using various medications (citalopram, escitalopram, carbamazepine, nefazodone, bupropion, valproate, naltrexone, tolcapone) for short periods of time (8 to 14 weeks) have demonstrated efficacy in approximately 70% to 75% of GD subjects. Seventeen double-blind, placebo-controlled pharmacotherapy studies have also been performed in GD, but the results of these studies have demonstrated mixed efficacy and tolerability.

Antidepressants

Hypotheses underlying the examination of antidepressant medications for GD are based on the neurobiology of GD and other impulse control disorders. Low levels of the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) and blunted serotonergic response within the ventromedial prefrontal cortex (vmPFC) have been associated with impulsive behaviors (Coccaro, 1996; Virkkunen, Goldman, & Nielsen, 1995). As compared with control comparison subjects, individuals with GD demonstrate diminished activation of the vmPFC when viewing gambling-related videotapes or during prepotent response inhibition when performing the Stroop color-word interference task (Potenza et al., 2003a, 2003b). Individuals with GD also show relatively diminished activation of the vmPFC during a simulated gambling task, and severity of gambling problem correlated inversely with signal intensity within this brain region (Reuter et al., 2005). In addition, levels of serotonin 1B receptor in the ventral striatum have been associated with problem gambling severity, suggesting that this receptor may in part contribute to differences in ventral striatal activity observed in GD (Potenza et al., 2013). Taken together, the findings suggest that drugs targeting serotonin neurotransmission may hold promise for the treatment of GD.

Of the 17 double-blind, placebo-controlled pharmacological studies in GD, 6 have examined SRIs. Clomipramine, an SRI that also inhibits norepinephrine reuptake, was the first SRI tested in a controlled fashion in GD. Hollander and colleagues (1992) reported a response to clomipramine in a single GD subject using a double-blind, placebo-controlled design. After receiving placebo for 10 weeks without

TABLE 25.1 Double-Blind, Placebo-Controlled Pharmacotherapy Trials for Gambling Disorder

Study	*Medication*	*Design/Duration*	*Subjects*	*Mean Daily Dose (± SD)*	*Outcome*
Hollander et al., 1992	Clomipramine	Parallel design 10 weeks	1 enrolled 1 completer	125 mg	90% improvement in gambling symptoms on medication
Saiz-Ruiz et al., 2005	Sertraline	Parallel design 6 months	60 enrolled 44 completers	95 mg	Similar improvement in both groups
Hollander et al., 2000	Fluvoxamine	Crossover 16-weeks with a 1-week placebo lead-in	15 enrolled 10 completers	195 mg (± 50)	Fluvoxamine superior to placebo
Blanco et al., 2002	Fluvoxamine	Parallel design 6 months	32 enrolled 13 completers	200 mg	Fluvoxamine not statistically significant from placebo
Kim et al., 2002	Paroxetine	Parallel design 8 weeks with 1-week placebo lead-in	53 enrolled 41completers	51.7 mg (± 13.1)	Paroxetine group significantly improved compared to placebo
Grant et al., 2003	Paroxetine	Parallel design 16 weeks	76 enrolled 45 completers	50 mg (± 8.3)	Paroxetine and placebo groups with comparable improvement
Grant & Potenza, 2006	Escitalopram	Open-label (12 weeks) with responders randomized to 8 weeks parallel design escitalopram or placebo	13 enrolled, all with co-occurring anxiety disorder and GD	25.4 mg (± 6.6)	Open-label reductions in anxiety and gambling and improvements appear to persist with active but not placebo drug
Black et al., 2007	Bupropion	Parallel design 12 weeks	39 enrolled 22 completers	324 mg	Bupropion and placebo groups demonstrated similar symptom improvement
Hollander et al., 2005	Lithium carbonate SR	Parallel design 10 weeks	40 Bipolar-spectrum patients enrolled 29 completers	1,170 mg (± 221)	Lithium group significantly improved compared with placebo
Kim et al., 2001b	Naltrexone	Parallel design 12 weeks with 1-week placebo lead-in	89 enrolled 45 completers	188 mg (± 96)	Naltrexone group significantly improved compared with placebo
Grant et al., 2008	Naltrexone	Parallel design 18 weeks with 1-week placebo lead-in (50 mg, 100 mg, 150 mg naltrexone vs. placebo)	77 enrolled 49 completers	Combined groups—no specific efficacious dose noted	Naltrexone group significantly improved compared with placebo on gambling and psychosocial function

(*continued*)

TABLE 25.1 (continued)

Study	*Medication*	*Design/Duration*	*Subjects*	*Mean Daily Dose (± SD)*	*Outcome*
Grant et al., 2006	Nalmefene	Parallel design 16 weeks	207 enrolled 73 completers	Fixed-dose study	Nalmefene 25 mg and 50 mg significantly improved compared to placebo
Grant et al., 2010	Nalmefene	Parallel design 16 weeks	233 enrolled 126 completers	Fixed dose study (20mg, 40mg, or placebo)	Initial analysis revealed no differences. Post-hoc analysis: 40 mg group significantly improved compared to placebo.
Grant et al., 2007	N-acetylcysteine (NAC)	Open-label with responders randomized to 6-weeks, parallel design NAC or placebo	27 enrolled 23 completers	1,476.9 mg (± 311.3)	NAC group had significant gambling symptom improvement in open-label phase; sustained in double-blind phase
Grant et al., 2014	NAC with imaginal desensitization	Parallel design 12 weeks	28 individuals with GD and nicotine dependence enrolled	1,200 mg to 3,000 mg	NAC + imaginal desensitization group significantly improved compared to placebo
Berlin et al., 2013	Topiramate	Parallel design 14 weeks	42 enrolled 27 completers	222.5 mg (± 108.5)	No differences between groups
McElroy et al., 2008	Olanzapine	Parallel design 12 weeks	42 enrolled 25 completers	8.9 mg (± 5.2)	Similar reductions in gambling symptoms in olanzapine and placebo groups
Fong et al., 2008	Olanzapine	Parallel design 7 weeks	23 enrolled 21 completers	2.5 mg to 10 mg	Similar reductions in gambling symptoms in olanzapine and placebo groups

response, the woman reported a 90% improvement in gambling symptoms after being treated with 125 mg/day of clomipramine. There have been no further controlled studies of clomipramine, however, to confirm the limited results of this initial study. In addition to its more common side effects (dry mouth, constipation, blurred vision, sexual dysfunction, weight gain, fine tremor, muscle twitching), clomipramine may also cause cardiac conduction problems and has significant drug–drug interactions.

In a double-blind, placebo-controlled study using sertraline, 60 subjects with GD were treated for 6 months (mean dose = 95 mg/day; Saiz-Ruiz et al., 2005). At the end of the study, 23 sertraline-treated subjects (74%) and 21 placebo-treated subjects (72%) were rated as responders based on the primary outcome measure (the outcome measure was the Criteria for Control of Pathological Gambling Questionnaire, a measure with good internal consistency and convergent validity), which assessed urges to gamble and gambling behavior. Sertraline did not demonstrate superiority to placebo. The authors presented only limited data on the psychometrics of their primary outcome measure. Sertraline was generally well tolerated, but, as with other antidepressants, it may cause sedation, constipation, weight gain, headache, sexual dysfunction, and dry mouth.

Only two SRIs have been examined in at least two randomized, placebo-controlled trials of GD. A double-blind, 16-week crossover study of fluvoxamine in 15 GD subjects demonstrated a statistically significant difference compared with placebo (Hollander et al., 2000). Interpretation of the study is complicated, however, by a phase-order treatment interaction (i.e., the medication did not separate from placebo during the first phase but did in the second phase). A 6-month double-blind, placebo-controlled trial of fluvoxamine in 32 gamblers failed to show statistical significance compared with placebo. The results of the latter study, however, are complicated by high rates of treatment discontinuation (only three subjects on medication completed the study) and a high placebo response rate (59%; Blanco, Petkova, Ibanez, & Saiz-Ruiz, 2002). Although differences in the results may be attributable to the temporal duration of each study, other design issues might also be important. For example, the study by Hollander and colleagues used the Pathological Gambling Modification of the Yale-Brown Obsessive Compulsive Scale (PG-YBOCS) as the primary outcome measure. The PG-YBOCS has demonstrated excellent validity and reliability in gambling treatment studies (Pallanti, DeCaria, Grant, Urpe, & Hollander, 2005). The study by Blanco and colleagues, however, used amount of money spent weekly as the primary outcome measure. These differences in outcome measures complicate the comparisons one can make between these two studies. Although fluvoxamine is generally well tolerated, it may result in gastrointestinal distress, sedation, mild anxiety, headache, increased urinary frequency, and sexual dysfunction. Fluvoxamine is a potent P450 1A2 inhibitor, and drug–drug interactions should be considered before it is prescribed.

As with fluvoxamine, studies have failed to demonstrate consistently the efficacy of paroxetine in treating GD. An initial double-blind, placebo-controlled study of paroxetine indicated its potential efficacy as a treatment for GD. Significant improvement was seen in subjects randomized to 8 weeks of treatment with paroxetine compared with those assigned to placebo (Kim, Grant, Adson, Shin, & Zaninelli, 2002). A larger multicenter, double-blind, placebo-controlled trial with patients with GD, however, failed to reproduce the results (Grant et al., 2003). In this second study, a high placebo response rate ("very much improved" or "much improved" based on the Clinical Global Improvement [CGI] scale) was observed: At study end, 48% of those assigned to placebo and 59% of those taking paroxetine were considered responders. Further study appears warranted to determine whether specific subgroups of individuals with GD (e.g., those with specific genetic characteristics) will respond preferentially to treatment with paroxetine or other SRIs. Consistent with this notion, preliminary data from an open-label escitalopram trial followed by double-blind randomization to active escitalopram or placebo phase suggest that individuals with GD and co-occurring anxiety disorders may benefit (on both measures of anxiety and gambling) from escitalopram (Grant & Potenza, 2006).

Although the randomized, placebo-controlled trials of antidepressants in GD have focused on medications with primarily serotonergic properties, one other antidepressant with a different mechanism of action has been tested. Bupropion (Black et al., 2007), a dopaminergic medication, was studied in 39 subjects during a 12-week period (mean dose = 324 mg/day). At the end of the study, both groups showed similar reductions in the PG-YBOCS, and five of

the bupropion-treated group (35.7%) and eight of the placebo-treated group (47.1%) were considered responders on the CGI scale. Bupropion was generally well tolerated but may cause headache, nervousness, stomach discomfort, and dry mouth.

Lithium

In one fluvoxamine study, two of three nonresponders worsened with active drug treatment and were observed to have symptoms of cyclothymia (Hollander et al., 1998). These findings suggested that an alternate medication, such as lithium, might be helpful for specific individuals with GD. In a double-blind, placebo-controlled study of 40 GD subjects with bipolar spectrum disorders (bipolar type II, bipolar not otherwise specified, or cyclothymia), sustained-release lithium carbonate (mean lithium level = 0.87 mEq/L) was shown to be superior to placebo in reducing GD symptoms during 10 weeks of treatment (Hollander, Pallanti, Allen, Sood, & Baldini Rossi, 2005). Although a majority (83%) of subjects in the treatment group displayed significant decreases in gambling urges, thoughts, and behaviors as measured by the PG-YBOCS, no differences were found in amount of money lost, episodes of gambling per week, or time spent per gambling episode. Active as compared with placebo drug was also superior in reducing symptoms of mania. Subjects in this study tolerated lithium without difficulty, but lithium may cause fine tremor, nausea, and diarrhea, and nephrotoxicity is possible when it is used chronically.

Opioid Antagonists

Opioid receptor antagonists inhibit dopamine release in the nucleus accumbens and ventral pallidum through the disinhibition of gamma-aminobutyric acid (GABA) input to the dopamine neurons in the ventral tegmental area (Broekkamp & Phillips, 1979; Phillips & LePiane, 1980; van Wolfswinkel & van Ree, 1985). As compared with control comparison subjects, individuals with GD show differences in nucleus accumbens activation during a simulated gambling task (Reuter et al., 2005). Although modulation of drive and subsequent behavioral output by dopamine, endorphin, and GABA have been investigated, the specific mechanisms underlying opioid receptor antagonism in specific patient groups such as those with GD remain incompletely understood.

A 12-week double-blind, placebo-controlled trial of naltrexone demonstrated superiority to placebo in 45 subjects with GD (Kim, Grant, Adson, & Shin, 2001b). Naltrexone (mean dose = 88 mg/day) was effective in reducing the frequency and intensity of gambling urges, as well as gambling behavior. A separate analysis of those subjects with at least moderate urges to gamble revealed that naltrexone was more effective in gamblers with more severe urges to gamble. The clinical use of naltrexone, however, is limited by significant side effects, as well as the occurrence of liver enzyme elevations, especially in patients taking nonsteroidal anti-inflammatory drugs (Kim, Grant, Adson, & Remmel, 2001a). More than 20% of subjects receiving active naltrexone developed abnormal liver function tests during a 12-week study (Kim, Grant, Adson, & Shin, 2001b). A second naltrexone study in 77 subjects randomized to either naltrexone or placebo over an 18-week period confirmed the findings of the initial study (Grant, Kim, & Hartman, 2008). Subjects assigned to naltrexone had significantly greater reductions in gambling urges and gambling behavior compared to subjects on placebo. Subjects assigned to naltrexone also had greater improvement in psychosocial functioning. By study endpoint, 39.7% of those on naltrexone were able to abstain from all gambling for at least 1 month, whereas only 10.5% on placebo attained complete abstinence for the same time period.

Two multicenter studies have further demonstrated the efficacy of opioid antagonists with the examination of nalmefene in the treatment of GD. In a large, multicenter trial using a double-blind, placebo-controlled, flexible-dose design, 207 subjects were assigned to receive 16 weeks of either nalmefene at varying doses (25, 50, or 100 mg/day) or placebo. At the end of the study, 59% of those assigned to nalmefene showed significant reductions in gambling urges, thoughts, and behavior compared to only 34% on placebo (Grant et al., 2006). The study, however, suffered from high rates of treatment discontinuation (63%). A second multicenter nalmefene study was performed with 233 participants using nalmefene (20 or 40 mg) or placebo (Grant, Odlaug, Potenza, Hollander, & Kim, 2010). In analyses performed using an intention-to-treat population, nalmefene failed to show statistically significant differences from placebo on primary and secondary outcomes. Post hoc

analyses of only participants who received a full titration of the medication for at least 1 week, however, demonstrated that nalmefene 40 mg/day resulted in significantly greater reductions on the primary outcome measure. These findings suggest that medication dosing may be an important consideration in achieving symptom control. One common side effect of opioid antagonists is nausea; these medications may also cause dizziness, insomnia, headaches, and loose stool. In addition, naltrexone, but not nalmefene, has been associated with a dose-dependent potential for hepatotoxicity.

Glutamate Agents

Because improving glutamatergic tone in the nucleus accumbens has been implicated in reducing the reward-seeking behavior in substance addictions (Kalivas, Peters, & Knackstedt, 2006), NAC, a glutamate-modulating agent, was administered to 27 GD subjects over an 8-week period, with responders randomized to receive an additional 6-week double-blind trial of NAC or placebo. Of those in the open-label phase, 59% experienced significant reductions in GD symptoms and were classified as responders. At the end of the double-blind phase, 83% of those assigned to receive NAC were still classified as responders compared to only 28.6% of those assigned to placebo (Grant, Kim, & Odlaug, 2007). A follow-up 12-week, double-blind, placebo-controlled study combining NAC with imaginal densensitization in 28 GD subjects who were also nicotine dependent found that NAC provided significant benefit compared to placebo on nicotine dependence symptoms during treatment and on gambling symptoms 3 months after formal treatment ended (Grant et al., 2014a).

Topiramate is a drug that is thought to influence mesolimbic dopamine transmission indirectly through GABAergic and glutamatergic mechanisms (Johnson, 2004). A 14-week, double-blind, placebo-controlled trial of topiramate in 42 subjects failed to show significant treatment effects for topiramate on the primary or secondary outcome measures (Berlin et al., 2013).

Atypical Neuroleptics

Two studies have examined the use of olanzapine in the treatment of GD. In a 12-week, double-blind, placebo-controlled trial of 42 subjects with GD, olanzapine (mean dose = 8.9 ± 5.2 mg) and placebo demonstrated similar reductions in gambling behavior and gambling urges (McElroy, Nelson, Welge, Kaehler, & Keck, 2008). Similarly, Fong and colleagues (2008) tested 23 GD subjects in a 7-week, double-blind, placebo-controlled trial and found similar reductions in cravings to gamble and gambling behavior in both the olanzapine and placebo groups.

Psychosocial Treatments

Current psychosocial treatment for GD involves multiple different options—brief interventions and individual and group CBT. All have demonstrated benefit in treating gambling disorders (Hodgins, Stea, & Grant, 2011). Although there is currently no agreed-upon standard-of-care for GD, the most widely studied psychological treatment for GD has been some form of CBT (Table 25.2). A meta-analysis identified 22 randomized trials published between 1968 and 2004 (Pallesen et al., 2005). This meta-analysis revealed that in general, psychological treatments were more effective than no treatment at both posttreatment (overall effect size = 2.01) and at follow-up averaging 17 months later (overall effect size = 1.59). A more recent meta-analysis that included 25 studies (Gooding & Tarrier, 2009) found that although there was considerable variability in the outcomes reported, posttreatment effects were generally positive for different types of therapy (e.g., behavioral, cognitive) and mode of therapy (e.g., individual, group, self-directed). To date, there are no randomized trials of inpatient treatment.

The majority of the psychosocial treatment literature for GD has focused on CBT techniques. The cognitive aspect includes psychoeducation, increased awareness of irrational cognitions, and cognitive restructuring. The behavioral techniques include identification of gambling triggers and the development of nongambling sources to compete with the reinforcers associated with gambling.

Cognitive Therapy

In a study of 40 subjects, individual cognitive therapy plus relapse prevention resulted in reduced gambling frequency and increased perceived self-control

TABLE 25.2 Controlled Psychological Treatment Trials for Gambling Disorder

Study	*Design/Duration*	*Subjects*	*Outcome*
Echeburúa et al., 1996	Stimulus control, in vivo exposure, relapse prevention vs. cognitive restructuring vs. combined treatment vs. waitlist/6 weeks with 12 month follow-up	64 enrolled 50 completers	At 12 months, 69% abstinence or much reduced in the first condition compared to 38% for cognitive restructuring or combined treatment
Milton et al., 2002	CBT vs. CBT + interventions, including positive reinforcement, barriers to change, problem-solving. Manualized. 8 weeks with 9 month follow-up.	40 enrolled 20 completers	No difference in outcome between treatments at 9-month follow-up, although both produced clinically significant change in the amount of money spent on gambling
Melville et al., 2004	1) Group CBT with/without mapping-enhanced treatment vs. waitlist control. 2) Mapping- enhancement treatment vs. waitlist control. Both 8 weeks.	1) 13 enrolled 2) 19 enrolled	CBT with mapping enhancement reported significant improvement; improvements sustained at 6-month follow-up
Marceaux et al., 2011	12-step procedures vs. CBT with mapping-enhancement vs. waitlist control	49 enrolled 44 completers	Both groups demonstrated significant improvement at the study end and 6-month study follow-up.
Wulfert et al., 2006	Cognitive–motivational–behavioral therapy (CMBT) vs. treatment as usual	21 enrolled 17 completers	CMBT group demonstrated significant improvements at a 12-month follow-up.
Sylvain et al., 1997	Cognitive therapy with relapse prevention vs. waitlist/30 sessions with 6-month follow-up	40 enrolled 14/22 in treatment group completed	36% improved on five variables compared to 6% on waitlist.
Ladouceur et al., 2001	Cognitive therapy + relapse prevention vs. waitlist/20 sessions with 12-month follow-up	88 enrolled 35/59 in treatment group completed	32% improved on four variables compared to 7% on waitlist.
Ladouceur et al., 2003	Group cognitive therapy + relapse prevention vs. waitlist/10 weeks with 2-year follow-up	71 enrolled 34/46 in treatment group completed	65% no longer met GD criteria compared to 20% for waitlist group.
Petry et al., 2005	Manualized CBT in individual counseling, vs. CBT workbook, vs. Gamblers Anonymous referral/ 8 sessions with 1-year follow-up	231 enrolled No data on completers	CBT was more effective than Gamblers Anonymous and individual counseling was more effective than workbook.
Dickerson et al., 1990	CBT workbook vs. workbook + a single in-depth interview	29 enrolled	Both groups showed improvement at 6 months.
Hodgins et al., 2001, 2004	CBT workbook vs. workbook + motivational enhancement intervention via telephone vs. waitlist	102 enrolled 85 available at 12 months	74% with motivational enhancement improved according to Clinical Global Impression compared to 61% with workbook and 44% on waitlist.
McConaghy et al., 1983	Aversion therapy vs. imaginal desensitization	20 enrolled 20 completers	Improvement in both groups over 12 months

McConaghy et al., 1988	Imaginal relaxation vs. imaginal desensitization	20 enrolled	Both groups improved after 1 week; however, treatment gains were not sustained at 12-month follow-up.
McConaghy et al., 1991	Aversion therapy vs. imaginal desensitization vs. in vivo desensitization vs. imaginal relaxation	120 enrolled 63 available 2 and 9 years later	Imaginal desensitization improved at 1 month and at 9 years
Grant et al., 2009a, 2011	Cue exposure with negative mood induction and imaginal desensitization with either individualized CBT or Gamblers Anonymous	68 enrolled 55 completed	64% of subjects receiving imaginal exposure + the negative mood induction vs. 17% of Gamblers Anonymous group were abstinent for 1 month. 77% of completers sustained improvements at 6-month follow-up.
Diskin & Hodgins, 2009	Single-session motivational interviewing (MI) + self-help workbook vs. workbook and talking to gambling interviewer for 30 minutes	81 enrolled 69 completers	The workbook + MI group reported less frequent gambling and with less money compared to the workbook-alone group at 1-year follow-up.
Oei et al., 2010	Individual vs. group CBT with 28 subjects assigned to waitlist control prior to intervention	102 enrolled	Individual CBT treatment resulted in better gambling symptom improvement; however, both treatments were effective in reducing gambling behavior compared to the waitlist control group.
Myrseth et al., 2009	Short-term group CBT (GCBT) vs. waitlist control	14 enrolled	85.7% of GCBT group had significant improvements in posttreatment gambling symptoms compared to 42.9% of a waitlist control.
Hodgins et al., 2007a	Detailed relapse prevention summary booklet mailed once or the same booklet with 7 additional informational booklets mailed over the next 12 months	169 enrolled	No group differences in gambling frequency or gambling losses at 12-month follow-up
Hodgins et al., 2009	Brief MI + mailed self-help workbook vs. workbook only vs. wait-list control	314 enrolled	MI + workbook and workbook-only groups reported significant decreases in gambling symptoms compared to the waitlist control.
Carlbring & Smits, 2008	Internet-based counseling vs. waitlist control	66 enrolled	Treatment group showed significant improvements in gambling symptoms as well as depression, anxiety, and overall quality of life.
Carlbring et al., 2012	Internet-based counseling vs. waitlist control	284 enrolled	Treatment group showed significant improvements in gambling symptoms as well as depression, anxiety, and overall quality of life. Maintained at 6-, 18- and 36 month follow-up.
Carlbring et al., 2010	MI vs. group CBT vs. waitlist	150 enrolled	MI and CBT groups reported significant improvement in gambling, depression, and anxiety symptoms.
Petry et al., 2009	10 minutes of brief advice, Motivational Enhancement Therapy (MET), MET + three sessions CBT, or no treatment (control group)	117 enrolled 113 completers	All treatments were equally effective in reducing gambling symptoms.

over gambling at 12 months when compared with a waitlist control group (Sylvain, Ladouceur, & Boisvert, 1997). Another study of cognitive therapy plus relapse prevention in 88 subjects also produced improvement in gambling symptoms compared with a waitlist group at 3 months that was maintained for 12 months (Ladouceur et al., 2001). Treatment discontinuation rates were high in both studies (37% and 47%, respectively), and the outcome analyses included only those subjects who completed the studies. Although the treatment was manualized, no measures of therapist competence and adherence were reported.

Group cognitive therapy has also been tested in 71 subjects with GD against a waitlist control condition (Ladouceur et al., 2003). Groups met for 2 hours weekly for 10 weeks. After ten sessions, 88% of those in group CBT no longer met GD criteria, compared with 20% in the waitlist condition. At the 24-month follow-up, 68% of the original group's cognitive therapy subjects still did not meet the criteria.

Although both individual and group cognitive therapies have shown promise in treating GD, rates of treatment discontinuation were high in these studies (up to 47%). In addition, the cognitive therapy studies have not yet determined the optimal number of sessions needed to reduce gambling symptoms and maintain improvement.

Cognitive-Behavioral Therapy

Although several trials have evaluated the efficacy of a purely cognitive approach, the largest number and the most rigorously designed trials have evaluated a combined CBT model. Although there is variability in the content and outcomes of CBT, positive effects have generally been found by different research groups.

A randomized study of CBT in GD compared four groups: (a) individual stimulus control and in vivo exposure with response prevention, (b) group cognitive restructuring, (c) a combination of (a) and (b), and (d) a waitlist control (Echeburúa, Baez, & Fernandez-Montalvo, 1996). At 12 months, rates of abstinence or minimal gambling were higher in the individual treatment group (69%) compared with group cognitive restructuring patients (38%) and the combined treatment group (38%). The same investigators further assessed individual and group relapse prevention for completers of a 6-week individual treatment program. At 12 months, 86% of those receiving individual relapse prevention and 78% of those receiving group relapse prevention had not relapsed, compared with 52% in the waitlist group.

One study compared CBT with CBT combined with interventions designed to improve treatment compliance (the interventions included positive reinforcement, identifying barriers to change, and applying problem-solving skills) in 40 subjects receiving eight sessions of manualized individual therapy. Only 35% of the CBT-alone group completed treatment compared with 65% of the CBT-plus-interventions group. At the 9-month follow-up, there was no difference in outcomes between treatments, although both produced clinically significant change (Milton, Crino, Hunt, & Prosser, 2002).

Melville and colleagues (2004) reported two studies that used a system targeting three topics (understanding randomness, problem solving, and relapse prevention) to improve outcome. In the first study, 13 subjects were assigned to 8 weeks of group CBT, group CBT with the topic-enhanced treatment, or a waitlist. In the second study, 19 subjects were assigned to a topic-enhanced group or a waitlist group for 8 weeks. For those subjects who were in the topic-targeting CBT group, significant improvement was maintained at both posttreatment and a 6-month follow-up (Melville, Davis, Matzenbacher, & Clayborne, 2004).

A large study described an eight-session manualized form of CBT where 231 subjects were randomized to weekly sessions with an individual counselor, the therapy in the form of a workbook, or referral to Gamblers Anonymous (Petry, 2005). Using an intent-to-treat analysis, the individual therapy and workbook reduced gambling behaviors to a greater degree than referral to Gamblers Anonymous.

In a study examining cognitive-motivational behavior therapy (CMBT), a method that combines gambling-specific CBT with motivational interviewing techniques to aid in resolving treatment ambivalence and improve retention rates, 9 subjects received manualized treatment and were compared with a control group of 12 subjects who received treatment as usual. All 9 subjects (100%) in the CMBT group completed treatment versus only 8 (66.7%) in the treatment-as-usual group. Significant improvements were observed at the 12-month follow-up in the CMBT group (Wulfert, Blanchard, & Freidenberg, 2006).

Cue Exposure

Cue exposure, based on classical conditioning, is a well-validated form of CBT used in the treatment of fear-based problems and has the goal of extinguishing the feared or learned response. The learned response is extinguished through repeated exposure to a conditioned stimulus in the absence of the feared consequence. The first randomized study compared imaginal desensitization (i.e., subjects were taught relaxation and then instructed to imagine experiencing and resisting triggers to gambling) with traditional aversion therapy (McConaghy, Armstrong, Blaszczynski, & Allcock, 1983). Both therapies had positive effects, but the imaginal desensitization was more successful in reducing gambling urges and behavior.

In a second study, 20 inpatient subjects were randomized to receive either imaginal desensitization or imaginal relaxation in 14 sessions over a 1-week period. Both groups improved at posttreatment, but the therapeutic gains were not maintained by either group at a 12-month follow-up (McConaghy, Armstrong, Blaszczynski, & Allcock, 1983).

In a larger study, 120 subjects were randomly assigned to aversion therapy, imaginal desensitization, in vivo desensitization, or imaginal relaxation. Subjects assigned to imaginal desensitization reported better outcomes at 1 month and up to 9 years later (McConaghy, Blaszczynski, & Frankova, 1991). This latter study, however, failed to follow up on approximately half of the subjects.

Using imaginal desensitization and combining cue exposure with negative mood induction, Grant and colleagues (2009a) examined 68 GD patients assigned to six sessions of treatment or Gamblers Anonymous. The negative mood induction involves focusing on the negative consequences of the problem behavior while the urge to engage in gambling is active. Individualized scripts were developed for each gambler, including gambling-related cues with the intention of activating each gamblers' urge via imagination (repeatedly listening to the script recorded). The scripts emphasized internal events, including thoughts and emotions experienced before, during, and after a gambling episode (e.g., euphoria before and during gambling and dysphoria and agitation after gambling). The pleasurable aspects of the script (i.e., anticipation of gambling and initial excitement) were then followed by the negative consequences of gambling unique to each gambler (negative mood induction). The study found that 64% of participants receiving imaginal exposure plus the negative mood induction as part of a six-session CBT program were able to maintain abstinence for 1 month, as opposed to only 17% of those randomly assigned to Gamblers Anonymous. For the CBT with imaginal exposure plus negative mood induction group, among those participants who responded to therapy after six sessions, 77% maintained their response for 6 months (Grant, Donahue, Odlaug, & Kim, 2011).

Brief Interventions

Brief treatments are not necessarily conceptualized as *treatment* by individuals who access them (Hodgins, Stea, & Grant, 2011) and therefore may be more appealing to gamblers who report significant ambivalence about stopping their behavior. Brief treatments may include single-session interventions, workbooks, or bibliotherapy.

In one study of brief interventions, Dickerson, Hinchy, and England (1990) randomly assigned 29 subjects either to workbook or to workbook plus a single in-depth interview. The workbook included cognitive-behavioral and motivational enhancement techniques. Both groups reported significant reductions in gambling at 6 months (Dickerson et al., 1990). Another study assigned gamblers to a CBT workbook, a workbook plus a telephone motivational enhancement intervention, or a waitlist. Rates of abstinence at 6 months did not differ among groups, although the frequency of gambling and money lost gambling were lower in the motivational intervention group (Hodgins, Currie, & el-Guebaly, 2001). Compared with the workbook alone, those gamblers assigned to the motivational intervention and workbook reduced gambling throughout a 2-year follow-up period (Hodgins, Currie, el-Guebaly, & Peden, 2004).

A study conducted by Diskin and Hodgins (2009) compared a single-session motivational interviewing module plus a self-help workbook with the workbook and speaking with an interviewer about gambling for 30 minutes. Half of the sample was randomized to each intervention. At the 12-month follow-up, those who received the motivational interviewing plus workbook gambled less and spent less money than the workbook-alone group (Diskin & Hodgins, 2009).

Motivational interviewing has been compared in individual versus group settings as well. Oei and colleagues (2010) randomized 102 gamblers to receive 6 weeks of individual or group CBT with motivational interviewing. At posttreatment and a 6-month follow-up, those completing the individual CBT program had better sustained outcomes in regard to gambling severity compared to the group CBT and waitlist control groups (although group CBT produced significant results vs. the waitlist control group as well) (Oei, Raylu, & Casey, 2010).

A study using a short-term group-CBT (GCBT) model for 14 subjects (78.6% male) found that 85.7% of the treatment group experienced significant improvements in posttreatment gambling symptoms compared to 42.9% of a waitlist control group (Myrseth, Litlerè, Støylen, & Pallesen, 2009). The other dependent variable, money spent gambling over the past week, however, failed to indicate any significant group differences, with 28.6% of both the GCBT and waitlist control groups experiencing improvement.

A study using a relapse-prevention bibliotherapy randomized 169 subjects who had recently quit gambling to receive either a summary booklet that detailed all available relapse-prevention information (single-mailing group) (n = 85) or to the same booklet plus seven additional informational booklets mailed over the next 12 months (repeated-mailing group) (n = 84) (Hodgins, Currie, el-Guebaly, & Diskin, 2007a). At the 12-month assessment, 24% of the repeated-mailing group reported using the strategies regularly to prevent relapse compared with 13% of the single-mailing group. Only 44% of the overall sample, however, reported not having gambled over the 3 months prior to the 12-month assessment.

Two self-directed motivational interventions were compared with a 6-week waitlist control and a workbook-only control in 314 GD patients (Hodgins, Currie, Currie, & Fick, 2009). Brief motivational treatment involved a telephone motivational interview and a mailed self-help workbook. Brief motivational booster treatment involved a telephone motivational interview, a workbook, and six booster telephone calls over a 9-month period. Both the brief and the brief booster treatment participants reported less gambling at 6 weeks than those assigned to the control groups. Participants in the brief booster treatment group, however, showed no greater improvement than brief treatment participants.

A similar combination of motivational interviewing and CBT was adapted to a Web-based format in which a therapist provides telephone support for individuals using online recovery materials (Carlbring & Smit, 2008). A waitlist control was compared with the 8-week Internet-based CBT program with minimal therapist contact via e-mail and weekly telephone calls of less than 15 minutes. The Internet-based intervention resulted in favorable changes in gambling, anxiety, depression, and quality of life. In a similar study, a larger sample of 284 GD subjects underwent an 8-week Internet-based CBT program with minimal therapist contact (average of 15 minutes per week and 4 hours throughout the entire program). The researchers found that gambling, depression, and anxiety symptoms decreased significantly following treatment and that treatment effects were maintained at 6-, 18- and 36-month follow-ups (Carlbring, Degerman, Jonsson, & Andersson, 2012).

A total of 150 primarily self-recruited patients with current gambling problems or GD were randomized to four individual sessions of motivational interviewing, eight sessions of CBT group therapy, or a no-treatment waitlist control. Treatment showed superiority in some areas over the no-treatment control in the short term, but no differences were found between motivational interviewing and group CBT at any point in time (Carlbring, Jonsson, Josephson, & Forsberg, 2010).

A randomized controlled study found that a 10-minute session of behavioral advice, one session of motivational enhancement therapy, or one session of motivational enhancement therapy plus three sessions of CBT were all equally effective in reducing gambling in a sample of 117 college students with either problem gambling or GD (Petry, Weinstock, Morasco, & Ledgerwood, 2009).

Family Therapy

A self-help workbook of the Community Reinforcement and Family Therapy (CRAFT) model, adapted for gambling, has been evaluated in two randomized controlled trials (Hodgins, Toneatto, Makarchuk, Skinner, & Vincent, 2007b; Makarchuk, Hodgins, & Peden, 2002). Family members are trained to use behavioral principles to reinforce nongambling behavior in individuals who are not addressing their gambling problem. Although positive effects

for family members and their gambling relatives were found in both trials, the studies found that behavioral principles were too complex for family members to implement without the support of a therapist.

A coping skills training program has also been evaluated for gambling. The program consists of 10 weekly individual sessions to teach more effective coping skills. A small (n = 23) randomized controlled trial comparing the coping skills program to a delayed treatment condition showed that partners of gamblers improved their ability to manage feelings of depression and anxiety. Partner gambling during that period decreased in both conditions but did not differ between them, nor did partner help seeking differ (Rychtarik & McGillicuddy, 2006).

Conclusions

Several conclusions can be drawn from the GD pharmacological and psychological treatment studies performed and published to date:

1. Although some pharmacotherapy and psychological treatment studies meet the criteria for a type 1 study, many GD studies have generally lacked a large enough sample for adequate statistical power. Exceptions to this would include the multicenter nalmefene studies (Grant et al., 2006, 2010) that were adequately powered at the time of enrollment and several of the CBT studies.
2. Although several different classes of medication have shown efficacy in treating GD in individual studies, only the opiate antagonists have had successful replication in randomized, placebo-controlled studies.
3. CBT has shown efficacy for GD, but no manualized CBT treatment has been examined in a confirmatory study by another independent investigator.
4. Different classes of medication seem equally effective in GD. No comparison studies of medications have been performed in a randomized, placebo-controlled design.
5. Both drug and behavioral treatments appear effective for GD. Few studies have systematically compared interventions or examined whether combinations of treatments are more beneficial. In addition, no study has examined whether certain individuals with GD would benefit differentially from specific pharmacotherapies or behavioral treatments.
6. Comparisons of treatment studies have generally been problematic due to the lack of consensus on appropriate outcome measure or measures.
7. With one exception, there have been no systematic dose-response studies for medication. The exception showed that nalmefene doses of 25 mg/day and 50 mg/day, but not 100 mg/day, were more effective than placebo (Grant et al., 2006).
8. CBT studies have shown that both brief interventions and longer-term therapy are potentially effective, but no study has yet examined the optimal duration of CBT.
9. The long-term effects of medication for GD remain largely untested. Only two studies have examined pharmacological effects for 6 months, but these studies experienced dropout rates of 59% (Blanco et al., 2002) and 44% (Saiz-Ruiz et al., 2005). No study has examined pharmacological treatment effects for longer than 6 months or whether the effects of acute treatment last beyond the 8 to 16 weeks.
10. There are limited data concerning the effectiveness of pharmacotherapy or CBT for GD subjects with co-occurring psychiatric conditions. Only scant preliminary data suggest that individuals with GD and bipolar symptoms respond to lithium (Hollander et al., 2005) and individuals with GD and nicotine dependence respond to NAC (Grant et al., 2014).

TRICHOTILLOMANIA

Trichotillomania has been defined as repetitive, intentionally performed pulling that causes hair loss and results in clinically significant distress or functional impairment. Trichotillomania appears relatively common, with an estimated prevalence between 0.6% and 3% (Christenson, Pyle, & Mitchell, 1991c; Duke, Keeley, Geffken, & Storch, 2010). The mean age of onset for trichotillomania is approximately 13 years (Mansueto & Rogers, 2012). Although prospective studies are lacking, the onset of trichotillomania has been associated with scalp disease and stressful life events (Mansueto & Rogers, 2012). Hair

pulling is subject to great fluctuations in severity, with worsening of symptoms often related to stress. Trichotillomania has traditionally been considered a disorder predominantly affecting females (Mansueto & Rogers, 2012) and is associated frequently with depression (39% to 65%), generalized anxiety disorder (27% to 32%), substance abuse (15% to 20%), and obsessive-compulsive disorder (13% to 23%; Christenson, Mackenzie, & Mitchell, 1991a).

Pharmacological Treatments

Several controlled pharmacological trials have been performed in trichotillomania (Table 25.3). Four of the eight double-blind pharmacological studies published to date have examined antidepressants, particularly SRIs. One study examined clomipramine compared with desipramine in a 10-week double-blind, crossover (5 weeks for each agent) design (following 2 weeks of single-blind placebo lead-in; Swedo et al., 1989). Twelve of 13 subjects had significant improvement on clomipramine.

Fluoxetine has been studied in three randomized trials with conflicting results. In one study, fluoxetine was compared with placebo in a 6-week double-blind crossover study (with a 5-week washout period between treatment arms; Christenson, Mackenzie, Mitchell, & Callies, 1991b). No significant differences were found between fluoxetine and placebo on measures of hair-pulling urges, frequency, or severity. In a study comparing fluoxetine with clomipramine, Pigott, L'Heueux, and Grady (1992) used a 2-week placebo lead-in followed by a double-blind, randomized 20-week crossover design (10 weeks on each agent). Both clomipramine and fluoxetine demonstrated a similar positive treatment effect (O'Sullivan, Christenson, & Stein, 1999). A third controlled study used a double-blind, placebo-controlled crossover design with 16 subjects treated with each agent for 12 weeks separated by a 5-week washout period (Streichenwein & Thornby, 1995). Fluoxetine failed to show significant improvement compared with placebo.

In one of the few studies to examine something other than an SRI, Christenson performed a placebo-controlled, 6-week, randomized, double-blind parallel-arm study of the opioid antagonist naltrexone (O'Sullivan et al., 1999). Of 17 subjects completing the study, 10 received placebo and 7 received 50 mg/day of naltrexone. Significant improvement was noted for the naltrexone group on one measure of trichotillomania symptoms (the NIMH Trichotillomania Symptom Severity Scale). However, although two other measures of symptom improvement (number of hair-pulling episodes and the NIMH Trichotillomania Impairment Scale) showed change in the anticipated direction for the naltrexone group, they failed to reach statistical significance.

A recent 8-week, double-blind study of naltrexone (dose titration from 50 mg to 150 mg/day) in 51 subjects using a standard outcome measure (the Massachusetts General Hospital Hair Pulling Scale) failed to find any difference on the outcome measure between naltrexone and placebo. Subjects taking naltrexone with a family history of addiction showed a greater numerical reduction in the urges to pull, although it was not statistically significant (Grant, Odlaug, Schreiber, & Kim, 2014b).

A study of NAC versus placebo was conducted in 50 adult subjects over a 12-week period. The study provided evidence that NAC is effective when compared with placebo; this finding was based on all primary outcome measures. The treatment effect was detected by 9 weeks (Grant, Odlaug, & Kim, 2009c). A similarly designed study in 39 children with trichotillomania, however, found no significant difference between NAC and placebo on any of the primary or secondary outcome measures (Bloch, Panza, Grant, Pittenger, & Leckman, 2013).

A double-blind, placebo-controlled study of olanzapine in 25 adults with trichotillomania found that 11 of 13 participants (85%) in the olanzapine group and 2 of 12 (17%) in the placebo group were considered responders according to the CGI but not on the more usually chosen outcome measure, the Massachusetts General Hospital Hair Pulling Scale. The mean dose of olanzapine at endpoint was 10.8 mg/day (Van Ameringen, Mancini, Patterson, Bennett, & Oakman, 2010).

Psychological Treatments

Behavioral interventions for trichotillomania have generally included three core elements: awareness training, stimulus control (which includes a variety of methods that serve to reduce the likelihood that pulling behavior begins), and competing response training (where patients are taught at the earliest sign of

TABLE 25.3 Double-Blind, Placebo-Controlled Pharmacotherapy Trials for Impulse Control Disorders

Impulse Control Disorder	*Medication*	*Design/Duration*	*Subjects*	*Mean Daily Dose (+SD)*	*Outcome*
Compulsive Buying					
Black et al., 2000	Fluvoxamine	Parallel design 9 weeks with 1-week placebo lead-in	23 enrolled 18 completers	220 mg	Fluvoxamine and placebo groups with comparable improvement
Ninan et al., 2000a	Fluvoxamine	Parallel design 13 weeks	37 enrolled 23 completers	215 mg (± 76.5)	Fluvoxamine and placebo groups with comparable improvement
Koran et al., 2003	Citalopram	7 weeks open-label followed by 9 weeks randomized	24 enrolled 15 completers	42.1 mg (± 15.3)	Citalopram group significantly improved compared to placebo
Trichotillomania					
Swedo et al., 1989	CMI vs. DMI	Crossover 5 weeks each agent	13 enrolled 13 completers	CMI: 180 mg (± 56) DMI: 173 mg (± 33)	CMI significantly greater improvement
Christenson et al., 1991b	Fluoxetine	Crossover 6 weeks fluoxetine and then placebo	21 enrolled 15 completers	Fixed titration to 80 mg	Fluoxetine not significantly different from placebo
O'Sullivan et al., 1999	CMI vs. fluoxetine	Crossover 10 weeks each agent	12 enrolled No data on number of completers	CMI: 200 mg ± 15 Fluoxetine: 75 mg ± 5	Similar significant improvement on both agents
Streichenwein & Thornby, 1995	Fluoxetine	Crossover 6 weeks on fluoxetine and placebo	23 enrolled 16 completers	70 mg	No differences between groups
Christenson et al., 1994	Naltrexone	Parallel design 6 weeks	No data on number enrolled 17 completers	50 mg	Naltrexone significant improvement on one measure
Grant et al., 2013	Naltrexone	Parallel design 8 weeks	51 enrolled 44 completers	50 mg, 100 mg, 150 mg	No differences between groups
Grant et al., 2009c (adults)	N-acetylcysteine (NAC)	Parallel design 12 weeks	50 enrolled 44 completers	1,200 mg to 2,400 mg/day	NAC group showed significant symptom improvement on primary outcomes

(*continued*)

TABLE 25.3 (continued)

Impulse Control Disorder	*Medication*	*Design/Duration*	*Subjects*	*Mean Daily Dose (+SD)*	*Outcome*
Trichotillomania					
Bloch et al., 2013 (Children)	NAC	Parallel design 12 weeks	39 enrolled 35 completers	1,200 to 2,400 mg/day	No differences between groups
van Ameringen et al., 2010	Olanzapine	Parallel design 12 weeks	25 enrolled 23 completers	10.8 mg (± 5.7)	Olanzapine significant improvement over placebo on primary measure
Intermittent Explosive Disorder					
Coccaro et al., 2009	Fluoxetine	Parallel design 12 weeks	100 enrolled 55 completers	29.8 ± 12.6 for responders	Fluoxetine group had sustained reduction in symptoms.
Hollander et al., 2003	Divalproex	Parallel design 12 weeks	109 subjects No data on number of IED subjects who completed	1,567 mg	Similar improvement in IED and placebo
Kleptomania					
Grant et al., 2009b	Naltrexone	Parallel design 8 weeks	25 enrolled 23 completers	116.7 mg (± 44.4)	Naltrexone was significantly superior to placebo.

CMI = clomipramine; DMI = desipramine.

pulling, or of the urge to pull, to engage in a behavior that is physically incompatible with pulling for a brief period of time until the urge subsides). Few controlled psychological treatment studies for trichotillomania have been published to date (Table 25.4). Azrin and colleagues randomized 34 subjects to either habit reversal therapy or negative practice (where subjects were instructed to stand in front of a mirror and act out motions of hair pulling without actually pulling; Azrin, Nunn, & Frantz, 1980). Habit reversal reduced hair pulling by more than 90% for 4 months, compared with 52% to 68% reduction for negative practice at 3 months. No control group was included, and therefore time and therapist attention could not be adequately assessed.

One study examined 25 subjects randomized to 12 weeks (10 sessions) of either acceptance and commitment therapy/habit reversal or waitlist (Woods, Wetterneck, & Flessner, 2006). Subjects assigned to the therapy experienced significant reductions in hair-pulling severity and impairment compared with those assigned to the waitlist, and improvement was maintained at the 3-month follow-up.

A recent study examined behavioral therapy in children with trichotillomania compared to a minimal attention control condition in 24 children for a period

TABLE 25.4 Controlled Psychological Treatment Trials for Impulse Control Disorders

Impulse Control Disorder	*Design/Duration*	*Subjects*	*Outcome*
Trichotillomania			
Azrin et al., 1980	Habit reversal therapy vs. negative practice	34 enrolled 34 completers	Habit reversal reduced hair-pulling by more than 90% for 4 months, compared to 52%–68% reduction for negative practice at 3 months.
Woods et al., 2005	Acceptance and commitment therapy/ habit reversal vs. waitlist	28 enrolled 25 completers	Improvement for acceptance and commitment therapy/habit reversal maintained at 3 months
Franklin et al., 2011 (children)	Behavioral therapy vs. minimal attention control (MAC)	24 enrolled	Behavior therapy resulted in significant improvements compared to MAC.
Ninan et al., 2000b	CBT vs. clomipramine vs, placebo	23 enrolled 16 completers	CBT was significantly more effective in reducing the symptoms of trichotillomania than either clomipramine or placebo.
Van Minnen et al., 2003)	Behavior therapy vs. fluoxetine vs. waitlist	43 enrolled 40 completers	Behavior therapy resulted in statistically significant reductions in trichotillomania symptoms compared to either fluoxetine or waitlist.
Moritz & Rufer, 2011	Decoupling compared to muscle relaxation	42 enrolled 38 completed	Decoupling movement resulted in significantly greater reductions in trichotillomania symptoms compared to the muscle relaxation group.
Compulsive Buying			
Mitchell et al., 2006	Group CBT vs. waitlist control	28 enrolled	Group CBT reported significantly greater reductions in number of buying episodes and time spent buying. Maintained at 6-month follow-up.
Mueller et al., 2008	Group CBT vs. waitlist control	60 enrolled	Group CBT produced significantly greater reductions on all outcome variables compared to those assigned to waitlist. Improvement maintained at 6-month follow-up.
Muller et al., 2011	Group CBT vs. telephone-guided self-help vs. waitlist control	56 enrolled	Group CBT had significantly better reduction of compulsive buying symptoms at study endpoint and 6-month follow-up.

of 8 weeks. Behavioral therapy produced a superior outcome compared with a condition that controlled for participation, nonspecific therapist contact effects, repeated assessments, and the passage of time. Upon completion of acute treatment at week 8, the behavioral therapy group's gains were maintained through an 8-week maintenance treatment phase (Franklin, Edson, Ledley, & Cahill, 2011).

Another study used "decoupling" techniques, in which the patient learns to perform actions that unlink the behavioral components involved in hair pulling. The researchers randomized 42 adults with trichotillomania to either decoupling or muscle relaxation training for 4 weeks. Upon completion of the study, subjects undergoing decoupling reported significantly greater reductions in their pulling urges and behaviors compared to the muscle relaxation group (Moritz & Rufer, 2011).

Comparison Studies

Although the studies of either pharmacological or psychological treatment are too few to recommend specific treatment approaches, two studies have used controlled design to compare treatment interventions. Ninan and colleagues used a placebo-controlled, randomized, parallel-treatment design to compare CBT and clomipramine (Ninan, Rothbaum, Marsteller, Knight, & Eccard, 2000b). Twenty-three subjects entered the 9-week study. The CBT was a modified manualized treatment based on the habit reversal therapy tested in a controlled study by Azrin and colleagues (1980). CBT was significantly more effective in reducing the symptoms of trichotillomania than either clomipramine or placebo. Although clomipramine resulted in greater symptom reduction than placebo, the difference was not statistically significant.

In a second comparison study, behavioral therapy was compared with fluoxetine in a 12-week randomized trial using a waitlist control (van Minnen, Hoogduin, Keijsers, Hellenbrand, & Hendriks, 2003). Forty-three subjects were enrolled (14 in behavior therapy, 11 in the fluoxetine group, and 15 in the waitlist). Behavior therapy resulted in statistically significant reductions in trichotillomania symptoms compared with either fluoxetine or waitlist.

Conclusions

Although there are many case reports on effective treatments for trichotillomania, the data from controlled trials are sparse. The one treatment that has shown potential promise in treating trichotillomania is habit reversal therapy, or some modification thereof. No manualized treatment, however, has been published in a confirmatory study by an independent investigator. Although habit reversal appears promising in the short term, there are no controlled trials examining the long-term effects of this treatment. NAC and olanzapine may benefit adults with trichotillomania, but there are conflicting data supporting the use of selective SRIs.

COMPULSIVE BUYING

Although not specifically recognized in the *DSM*, the following diagnostic criteria have been proposed for compulsive buying: (a) maladaptive preoccupation with or engagement in buying (evidenced by frequent preoccupation with or irresistible impulses to buy; or frequent buying of items that are not needed or not affordable; or shopping for longer periods of time than intended); (b) preoccupations or the buying itself lead to significant distress or impairment; and (c) the buying does not occur exclusively during hypomanic or manic episodes (McElroy, Keck, Pope, Smith, & Strakowski, 1994).

The onset of compulsive buying typically occurs during late adolescence or early adulthood (Black, 1996). The disorder appears more common among females (Black, 1996; Christenson et al., 1994). Individuals with compulsive buying report repetitive, intrusive urges to shop that are often triggered by being in stores and worsen during times of stress, emotional difficulties, or boredom. Compulsive buying regularly results in substantial financial debt, marital or family disruption, and legal consequences (Christenson et al., 1994). Guilt, shame, and embarrassment typically follow the buying episodes. Most items are not used or even removed from the packaging (Christenson et al., 1994).

Pharmacological Treatments

The effectiveness of pharmacotherapy in treating compulsive buying has been examined in three

double-blind, randomized, placebo-controlled trials (see Table 25.3). In the first of two double-blind fluvoxamine studies, 37 subjects were treated for 13 weeks. Only 9 of 20 patients assigned to medication were responders (mean dose = 215 mg/day), and this rate did not differ significantly from that in the placebo group (8 of 17 were responders; Ninan et al., 2000a). In the second double-blind study, Black and colleagues treated 23 patients for 9 weeks following a 1-week placebo lead-in phase. Using a mean dose of 200 mg/day, no differences in response rates were observed between the groups treated with active drug or placebo (Black, Gabel, Hansen, & Schlosser, 2000).

The third controlled study was a 7-week open-label study of citalopram that randomized the responders to 9 weeks of double-blind medication or placebo (Koran, Chuong, Bullock, & Smith, 2003). Subjects taking citalopram demonstrated statistically significant decreases in the frequency of shopping and the intensity of thoughts and urges concerning shopping.

Psychological Treatments

There have been three randomized psychosocial treatment studies for compulsive buying (see Table 25.4). The first study assigned 28 subjects to either group CBT or a waitlist condition. After 10 weeks (which included 12 sessions of therapy), those assigned to the group CBT reported significantly greater reductions in the number of buying episodes and the time spent buying. The results were maintained for 6 months following treatment discontinuation (Mitchell, Burgard, Faber, Crosby, & de Zwaan, 2006).

A second study of group CBT using weekly sessions for 12 weeks found that those assigned to group CBT ($n = 31$) reported significantly greater reductions on all outcome variables compared to those assigned to a waitlist ($n = 29$). The improvement was noted both at the end of the study and again at the 6-month follow up (Mueller et al., 2008).

A third study compared group CBT to telephone guided self-help and to a third condition of waitlist in 56 subjects over a 10-week period. Those assigned to group CBT did significantly better in the reduction of compulsive buying symptoms compared to the other two groups at study endpoint and at the 6-month follow-up (Muller, Arikian, de Zwaan, & Mitchell, 2011).

Conclusions

There is scant evidence concerning effective pharmacological treatments for compulsive buying. Based on available data, citalopram may offer some benefit for this disorder, although the study suffers from several major limitations—small sample in the randomized phase ($n = 15$), a diagnostic instrument without sufficient psychometrics, and outcome measures that lack validity and reliability data.

Current data strongly support the use of group CBT for compulsive buying. The studies have replicated a group CBT approach, although not by independent investigators. The treatment effects have also been shown to persist after treatment is concluded.

INTERMITTENT EXPLOSIVE DISORDER

IED is defined by recurrent, significant outbursts of aggression, often leading to assaultive acts against people or property, which are disproportionate to outside stressors and not better explained by another psychiatric diagnosis. Recent research suggests IED may be common, with 6.3% of a community sample meeting criteria for lifetime IED (Coccaro et al., 2004).

IED symptoms tend to start in adolescence and appear to be chronic (Coccaro, Schmidt, Samuels, & Nestadt, 2004; McElroy, Soutullo, Beckman, Taylor, & Keck, 1998). Individuals with IED regard their behavior as distressing and problematic (McElroy et al., 1998). Outbursts are generally short-lived (usually less than 30 minutes in duration) and frequent (multiple times per month; McElroy et al., 1998). Legal and occupational difficulties are common (McElroy et al., 1998).

Pharmacological Treatments

Pharmacological treatment data for IED are limited (see Table 25.3). Although pharmacotherapies have been studied in the treatment of aggression, impulsivity, and violent behavior, there are only two controlled studies specific to IED.

A double-blind, randomized, placebo-controlled trial of fluoxetine in 100 individuals with IED found that fluoxetine treatment resulted in a sustained reduction in aggression and irritability as early as the second week of treatment. Full or partial remission of impulsive aggressive behaviors occurred in

46% of fluoxetine-treated subjects (Coccaro, Lee, & Kavoussi, 2009).

In a randomized, double-blind, placebo-controlled study, 96 subjects with Cluster B personality disorders, 116 subjects with IED, and 34 subjects with posttraumatic stress disorder were randomized to divalproex sodium or placebo for 12 weeks of treatment. Using an intent-to-treat analysis, the study found that divalproex had no significant influence on aggression in the subjects with IED (Hollander et al., 2003).

Psychological Treatments

Although case reports suggest that insight-oriented psychotherapy and behavioral therapy may be beneficial, there are no controlled psychological treatment studies in IED (McElroy et al., 1998).

Conclusions

Although there is a paucity of type 1 or 2 treatment studies for IED, the fluoxetine study suggests that fluoxetine may be an effective treatment for IED. There are only case reports of psychological treatments. IED is a disabling disorder with significant public health issues. Treatment studies for this disorder are needed.

KLEPTOMANIA

Kleptomania is characterized by repetitive, poorly controlled stealing of items not needed for personal use. Kleptomania begins most often in late adolescence or early adulthood (McElroy, Pope, Hudson, Keck, & White, 1991). The course of the illness is generally chronic, with waxing and waning of symptoms. Women appear twice as likely to suffer from kleptomania as men (Grant & Kim, 2002). Individuals with kleptomania frequently hoard, discard, or return stolen items (McElroy et al., 1991).

Most individuals with kleptomania try unsuccessfully to stop stealing. The difficulties with stopping the behavior often lead to feelings of shame and guilt (Grant & Kim, 2002). Many individuals with kleptomania (64% to 87%) have been apprehended at some time due to their stealing behavior (McElroy et al., 1991, with a smaller percentage (15% to 23%) having been jailed (Grant & Kim, 2002).

Pharmacological Treatments

There has been only one randomized, placebo-controlled study of medication in the treatment of kleptomania. An 8-week, double-blind, placebo-controlled trial was conducted to evaluate the safety and efficacy of oral naltrexone in 25 subjects with kleptomania (Grant, Kim, & Odlaug, 2009b). Naltrexone dosing ranged from 50 mg/day to 150 mg/day. Subjects assigned to naltrexone had significantly greater reductions in K-YBOCS total scores, stealing urges, and stealing behavior compared with subjects on placebo. The mean effective dose of naltrexone was 116.7 (± 44.4) mg/day. Naltrexone was well tolerated, with minimal nausea, and produced no elevated liver enzymes.

Psychological Treatments

No controlled studies of psychological treatments exist for kleptomania. Case reports suggest that cognitive and behavioral therapies may be effective in treating kleptomania. Undergoing seven sessions of covert sensitization combined with exposure and response prevention over a 4-month period, a young man was able to reduce his stealing frequency (Guidry, 1969). In another case of covert sensitization, a young woman underwent five weekly sessions wherein she was instructed to practice covert sensitization whenever she had urges to steal. She was able to then go 14 months with only a single lapse in behavior and with no reported urges to steal (Gauthier & Pellerin, 1982). Imaginal desensitization in 14 15-minute sessions over 5 days resulted in complete remission of symptoms for a 2-year period for two subjects (McConaghy & Blaszczynski, 1988).

Conclusions

There is one controlled study of naltrexone in kleptomania and it would suggest that naltrexone may be a beneficial treatment for this disorder. No controlled trials of psychosocial interventions have been reported. The current psychological research is based primarily on case reports.

The research on treatment outcome in kleptomania contrasts sharply with the quantity and quality of studies in GD. This state of affairs is probably attributable to the low prevalence of kleptomania and to

clinical difficulties in treating individuals involved in illegal activities. Nevertheless, there is a substantial need for systematic studies of the treatment of this disorder. Such studies may need to involve collaboration across multiple treatment centers in view of the disorder's low prevalence.

RECOMMENDATIONS BASED ON TREATMENT OUTCOME LITERATURE

In the areas of GD and impulse control disorders, the systematic study of treatment efficacy and tolerability is in its infancy. With few studies published yet that even approximate a type 1 study, it is not possible to make treatment recommendations with a substantial degree of confidence. No drugs are currently approved by the U.S. Food and Drug Administration for the treatment of any of the impulse control disorders. Nonetheless, specific drug and behavioral therapies offer promise for the effective treatment of GD. Treatment studies in GD are substantially limited. Most published studies have employed relatively small sample sizes, are of limited duration, and involve possibly nonrepresentative clinical groups (e.g., those without co-occurring psychiatric disorders). In addition, response measures have varied across studies, in part because the definition of "response" in GD treatment remains debated. Heterogeneity of treatment samples may also complicate identification of effective treatments. At present, issues such as which medication to use and for whom or the duration of pharmacotherapy or CBT cannot be sufficiently addressed with the available data. Two consistent findings across treatment studies, the high rates of placebo response and study discontinuation, and identification of factors related to placebo response and treatment discontinuation, would help inform future studies and advance treatment strategies for the disorder.

For the impulse control disorders, there are fewer available data to generate empirically supported treatment recommendations. For trichotillomania, habit reversal therapy, NAC, and olanzapine may be beneficial, but the evidence is based on only a few studies with small samples, each using a different variation of habit reversal therapy and, in the cases of two studies, lacking a control group. Although there is less evidence for effective treatments for compulsive buying, IED, or kleptomania, group CBT appears promising for compulsive buying, naltrexone may be beneficial for kleptomania, and fluoxetine may be beneficial for IED.

In conjunction with emerging epidemiological data supporting a relatively high prevalence of impulse control disorders, the small amount of empirical data in the area of effective treatments for impulse control disorders highlights the clinical need for additional research in this area.

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26

Treatments for Neurocognitive Disorders

Pei Huey Nie
David L. Sultzer

Dementia, or neurocognitive disorders, refers to a number of clinical syndromes originating in brain pathology and characterized by cognitive deficits and functional impairment. Various definitions exist in an attempt to standardize the criteria. However, the diagnosis of dementia is ultimately a clinical one and includes a multidimensional perspective. As such, the treatment of dementia requires a comprehensive approach.

INTRODUCTION

Reports of dementia prevalence and incidence vary depending upon region and study methodology. Alzheimer's disease (AD) is widely considered the most common cause of dementia. AD accounts for about 60% to 80% of all dementia types in the United States, affecting approximately 5.4 million Americans ("Alzheimer's disease facts and figures," 2012). One in eight Americans age 65 or older and 45% of Americans over the age of 85 have AD. Consequently, it is the dementia type most studied and therefore the subject of a large portion of this chapter. Vascular dementia is the second most common type of dementia, followed by mixed-type dementia, also known as AD with cerebrovascular disease, dementia with Lewy bodies, and frontotemporal dementias (Table 26.1; Fratiglioni, De Ronchi, & Aguero-Torres, 1999; Schneider, Arvanitakis, Bang, & Bennett, 2007).

Dementia is distinct from other mental disorders because the neuropathological etiology is relatively better understood. Regardless of neurobiology, however, the behavioral manifestations, psychological impact, and consequent impact on lifestyle and interpersonal interactions can be similar to any primary psychiatric illness. Given the biopsychosocial model approach and need for ongoing care, mental health professionals are well suited to treat dementia and the associated symptoms.

Diagnostic Criteria

In 2013, the American Psychiatric Association released the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*-5), in which "dementia" is included within the newly named entity "neurocognitive disorders." Major and mild neurocognitive disorders are largely differentiated by two factors: (1) the severity of cognitive decline from a previous level of performance in one or more of the six defined cognitive domains and (2) whether cognitive deficits interfere with independence in daily activities. Features of major and mild neurocognitive disorders are shown in Table 26.2.

Etiologic specifiers are provided within each category of disorder. Specifiers are Alzheimer's disease, frontotemporal lobar degeneration, Lewy body disease, vascular disease, traumatic brain injury, substance/medication use, HIV infection, prion disease, Parkinson's disease, Huntington's disease, another medical condition, multiple etiologies, and unspecified. Criteria for clinical syndromes due to AD are shown in Table 26.3.

TABLE 26.1 Common Types of Dementia

Dementia Syndrome	*Key Clinical Features*
Alzheimer's dementia	• Insidious onset, gradual progression • Early deficits in recent memory, language, and visuoperceptive skills • Apathy and depression early in course • Psychosis and agitation later in course
Vascular dementia	• May be abrupt in onset with acute stroke • Small vessel cerebrovascular disease is more common, with gradual progression. • Variable deficits, depending on location of cerebrovascular disease • Forgetfulness, executive deficits, and poor concentration are common. • Often with depression, apathy, psychomotor slowing, motor/sensory signs, gait disturbance • Evidence of cerebrovascular disease by history, exam, or neuroimaging
Dementia with Lewy bodies	• Fluctuating cognition with varying attention, visuoperceptive deficit, visual hallucinations, and parkinsonism • Supportive features: falls, syncope, transient loss of consciousness, REM sleep changes, delusions
Mixed dementia	• Clinical features of both AD and another type of dementia
Parkinson's disease with dementia	• Tremor, rigidity, and bradykinesia precede cognitive deficits. • Cognitive slowing, forgetfulness, and executive deficits are common.
Frontotemporal dementia	• Early changes in personality and behavior: disinhibition, apathy, anxiety, lability, inflexibility, repetitive behaviors • Poor attention, distractible, executive deficits • Variable language impairment • Gradual progression of behavioral symptoms and cognitive deficits

In 2011, the National Institute of Aging and Alzheimer's Association introduced revised criteria for the diagnosis of all-cause dementia and for AD dementia. Further, they classified AD into three phases: preclinical phase, mild cognitive impairment due to AD, and dementia due to AD (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). Dementia due to AD is further divided into the categories of probable AD dementia, possible AD dementia, and probable or possible AD dementia with evidence of the AD pathophysiological process. The prodromal AD diagnostic criteria are based on clinical biomarkers and are intended to inform future classifications and treatments.

Summary of Chapter

The treatment of dementia is currently symptomatic in that the goal is to temporarily improve symptoms or slow the progression of cognitive, psychiatric, and behavioral symptoms. The understanding of dementia neuropathology is growing, and along with it, opportunities are increasing for psychopharmacological intervention. This chapter addresses treatments for two aspects of neurocognitive disorders. First, we review current pharmacological interventions that can temporarily slow the decline of cognitive deficits. Second, we include a review of the

TABLE 26.2 Major Versus Mild Neurocognitive Disorders (NCD)

	Major NCD	*Mild NCD*
1. Cognitive decline, as described by:		
a. Concern of cognitive decline by individual, informant, or clinician	Significant decline	Mild decline
b. Cognitive performance by standardized testing or other quantifiable assessment	Substantial impairment	Modest impairment
2. Interference with independence	Yes	No, but compensatory arrangements may be necessary

TABLE 26.3 Major Versus Mild Neurocognitive Disorder (NCD) Due to Alzheimer's Disease

	Major NCD due to AD	*Mild NCD due to AD*
A. Criteria met for:	Major NCD	Mild NCD
B. Insidious onset and gradual progression of impairment in:	At least two cognitive domains	One or more cognitive domains
C. Criteria met for probable AD or possible AD	*Major NCD due to probable AD* is diagnosed if there is:	*Mild NCD due to probable AD* is diagnosed if there is:
	1. Evidence of a causative AD genetic mutation from family history or genetic testing, OR	Evidence of a causative AD genetic mutation from family history or genetic testing
	2. All three present: a. Decline in memory and learning and at least one other domain, based on history or serial testing b. Steadily progressive, gradual decline in cognition, without extended plateaus c. No evidence of mixed etiology	
	Possible AD is diagnosed if neither of above 2 items is met.	*Possible AD* is diagnosed if there is no evidence of a causative AD genetic mutation from family history or genetic testing, AND All three present: 1. Decline in memory and learning 2. Steadily progressive, gradual decline in cognition, without extended plateaus 3. No evidence of mixed etiology
D. Not better otherwise explained by cerebrovascular disease, other neurodegenerative disease, substances, or other mental, neurological or systemic disorder.		

management of behavioral and psychological symptoms, also described as neuropsychiatric symptoms, that are associated with dementia syndromes. Lastly, we include a review of disease-modifying treatments in development that may beneficially alter the course of disease, or reduce or prevent symptom expression in those at risk.

TREATMENT OF ALZHEIMER'S DEMENTIA

The central pathological feature of AD is the presence of neuritic plaques, consisting primarily of β-amyloid peptide aggregates, and neurofibrillary tangles, composed of tau molecule aggregates (Querfurth & LaFerla, 2010). The focus of AD treatment has been to target the biochemical abnormalities that result from the subsequent nerve cell loss. For instance, cholinesterase inhibitors enhance cholinergic transmission by inhibiting the breakdown of acetylcholine, and memantine is thought to attenuate toxic effects of glutamate. These treatments are considered symptomatic.

While cholinesterase inhibitors and memantine are standard treatments for AD at this time, the referenced literature demonstrates only modest benefit and critics cite the variability in methodological quality of the trials (Kaduszkiewicz, Zimmermann, Beck-Bornholdt, & van den Bussche, 2005). Further, the AD2000 Collaborative Study concluded that donepezil, the most commonly prescribed cholinesterase inhibitor, provides little overall benefit and is not cost-effective. Small improvements in cognition and functional abilities were detected between groups receiving donepezil and placebo, as reflected in the 0.8-point increase in the Mini-Mental State Examination (MMSE) result and 1.0-point increase in the Bristol Activities of Daily Living Scale score. However, no improvement was detected on institutionalization rates or progression of disability

(Courtney et al., 2004). The United Kingdom's National Institute for Health and Clinical Excellence (*Dementia: A NICE-SCIE Guideline on Supporting People With Dementia and Their Carers in Health and Social Care*, 2007) also commented on the significant but relatively small evidence for dementia medication effectiveness. However, in 2011 they published guidance that increased the accessibility of dementia medications, compared to their earlier recommendation (National Institute for Health and Care Excellence, 2011).

The study designs for the more salient clinical trials are type 1, randomized, double-blinded, and placebo-controlled and usually 6 months in duration. Analyses discussed in this chapter are type 1 studies or type 4 systematic reviews or meta-analyses, unless otherwise specified. Rating scales are used in each study to measure primary and secondary outcomes. Dementia medication trials usually assess global function, cognitive performance, activities of daily living (ADLs)/functioning, behavioral disturbance, and tolerability. Rating scales most commonly used in trials include the following. For cognitive function:

- Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog): 70-point scale that measures cognitive performance, including common cognitive deficits in AD
- Severe Impairment Battery (SIB): 100-point scale designed to assess cognitive skills in those with more advanced AD
- MMSE: 30-point scale used to measure global cognitive deficits; the most widely used screening instrument in AD studies

For global assessment:

- Global Rating/Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus): uses the process of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). Measures global change based on a rater's evaluation of cognitive, functional, and behavioral symptoms through an independent semistructured clinical interview of the patient and the patient's caregiver.
- Global Deterioration Scale (GDS): measures overall illness severity and incorporates cognition, self-care, and ADLs

For ADLs:

- Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL): designed to assess basic and complex tasks over a broad range of severity in patients with AD

For behavioral disturbance:

- Neuropsychiatric Inventory (NPI): a 10-item scale: delusions, hallucinations, agitation/aggression, depression, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/liability, aberrant motor behavior

CHOLINESTERASE INHIBITORS

The cholinesterase inhibitors donepezil, rivastigmine, and galantamine are considered first-line pharmacological treatments for dementia and have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of mild to moderate AD. In 2006, donepezil received additional approval for severe AD. Typical adverse side effects of cholinesterase inhibitors are gastrointestinal and dose-related. The frequency of gastrointestinal adverse side effects ranges between 3% and 50% across clinical trials (Gauthier, 2001). The severity of adverse effects is usually mild, and their frequency declines after a few weeks. Less common but notable class-related adverse effects include bradycardia and syncope related to vagotonic cholinergic effects, aggression and sleep disturbance related to central nervous system involvement, and urinary incontinence from parasympathetic mechanisms. The dosage is titrated gradually to minimize the risk of adverse side effects (Inglis, 2002)

Donepezil

Pivotal Trials and Key Findings

The two pivotal trials in mild to moderate AD were conducted in the 1990s and lasted 12 to 24 weeks. Primary outcome measures included the ADAS-cog and CIBIC-plus. A small but statistically significant benefit was detected on both scales for donepezil-treated versus placebo-treated participants (Rogers, Doody, Mohs, & Friedhoff, 1998; Rogers,

Farlow, Doody, Mohs, & Friedhoff, 1998). A more recent clinical trial investigating the 23-mg dose used the SIB and CIBIC-plus as primary outcome measures. Compared to the group receiving 10 mg of donepezil, the higher dose was associated with improved cognition on the SIB. However, only in post hoc analyses and between severely advanced and less impaired patients was there a significant improvement on both SIB and CIBIC-plus scales. The 23-mg group reported 10% more adverse effects than the 10-mg group, primarily nausea, dizziness, and vomiting (Farlow et al., 2010)

In a 12-month study, both the donepezil and placebo groups declined on the global assessment scale by week 52, but the donepezil group exhibited less cognitive decline on the MMSE (by 2.2 points) compared to placebo (Winblad et al., 2001). The authors suggested that donepezil had delayed cognitive decline by almost 1 year. In a study of 531 patients with moderate dementia, a survival analysis found that donepezil prolonged the onset of clinically evident functional decline by 5 months compared to placebo (Mohs et al., 2001).

Meta-analyses and Recent Updates

A 2006 meta-analysis summarized findings from 15 clinical trials that included 4,406 total participants. Trials lasted 24 to 52 weeks and included patients with mild, moderate, and severe AD. Overall, there was benefit from donepezil treatment in the cognitive and global clinical domains. Improvement in ADLs and behavior domains was observed but was less substantial. Although efficacy was demonstrated, the recommendation for donepezil treatment is not unanimous given the relatively small treatment effects, cost-benefit ratios, and real-life clinical relevance (Birks & Harvey, 2006).

A systematic review of cholinesterase inhibitors for AD published in 2005 included 12 randomized controlled trials studying donepezil (Kaduszkiewicz et al., 2005). Improved cognition, measured with the ADAS, ranged between 1.5 and 3.9 points. (For reference, the FDA proposes that a 4-point minimum difference would indicate a clinically important effect based on expert opinion.) Differences on the CIBIC ranged between 0.26 and 0.54 points, which can be interpreted as modest at best.

Clinical Use

Donepezil is the first of the second-generation cholinesterase inhibitors used for dementia treatment (Table 26.4). It is also the most widely prescribed dementia medication. It appears to induce, on average, a small improvement in cognition and overall clinical symptoms. The treatment effect size and tangible effectiveness make the positive results less than resounding.

Rivastigmine

Pivotal Trials and Key Findings

The pivotal trials for rivastigmine capsules were also conducted in the 1990s and lasted 26 weeks. Primary efficacy measures were the ADAS-cog, CIBIC-plus, and Progressive Deterioration Scale. Both trials demonstrated a small but statistically significant benefit in cognition and global clinical ratings, but only one trial demonstrated significant improvement in ADLs (Corey-Bloom, Anand, & Veach, 1998; Rösler et al, 1999).

Transdermal rivastigmine has been studied in more recent trials. In a 6-month double-blind, placebo-controlled study of transdermal rivastigmine, 1,195 patients with mild to moderate AD were randomized to one of four treatment groups: placebo,

TABLE 26.4 Donepezil

Pharmacology	Noncompetitive, reversible cholinesterase inhibitor with greater selectivity for acetylcholinesterase than butyryl cholinesterase
Usual dosing	Donepezil 10 mg/day
Dosage forms available	Donepezil: 5-, 10-mg tablets; 5-, 10-mg oral disintegrating tablets. Aricept: 5-, 10-, 23-mg tablets; 5-, 10-mg oral disintegrating tablets
FDA-approved indications	Mild, moderate, and severe AD
Adverse effects	Nausea, vomiting, diarrhea, weight loss, vivid dreams

12 mg/day capsule rivastigmine, 10 cm^2 (9.5 mg/24 hours) transdermal rivastigmine, or 20 cm^2 (17.4 mg/24 hours) transdermal rivastigmine. Primary efficacy measures were the ADAS-cog and ADCS-CGIC. Both transdermal patch groups and the capsule group demonstrated improvement on the ADAS-cog compared to placebo. However, on the ADCS-CGIC, there were significant treatment differences between the 10-cm^2 patch and capsule compared to placebo but not between the 20-cm^2 patch and placebo. Rates of nausea and vomiting were significantly lower in groups receiving the 10-cm^2 transdermal patch compared to capsules. However, rates of these adverse effects were similar between groups receiving the capsules and 20-cm^2 patch, and they were higher in both compared to the 10-cm^2 patch (Winblad et al., 2007).

In 2013, the FDA expanded the transdermal rivastigmine indication to include severe AD based on the ACTION (ACTivities of Daily Living and CognitION) study. This double-blind, parallel-group, non–placebo-controlled trial randomized 716 patients with severe AD to receive either the 5-cm^2 (4.6 mg/24 hours) patch or the 15-cm^2 (13.3 mg/24 hours) patch. Primary efficacy measures included SIB and the ADCS-ADL-SIV, the severe impairment version. At week 24, the higher-dose group demonstrated greater improvement on both measures without a significant increase in adverse effects (Farlow, Grossberg, Sadowsky, Meng, & Somogyi, 2013).

The pivotal trial that examined rivastigmine in dementia associated with Parkinson's disease was a 24-week placebo-controlled trial involving 541 patients with mild to moderate dementia diagnosed 2 years or more after a Parkinson's disease diagnosis. Patients were randomized to receive placebo or a 3- to 12-mg/day dose of rivastigmine (mean dosage = 8.6 mg/day). Primary efficacy measures were ADAS-cog and ADCS-CGIC. Rivastigmine-treated groups demonstrated significant improvements on both measures compared to placebo but also exhibited more adverse effects, including tremor. Tremor was reported by 10.2% of patients in the rivastigmine group and 3.9% in the placebo group (Emre et al., 2004).

Meta-analyses and Recent Updates

A meta-analysis reviewed results of 13 randomized controlled trials studying rivastigmine in a total of 512 participants (Birks, Grimley Evans, Iakovidou, & Tsolaki, 2009). After 26 weeks of treatment with 6 to 12 mg/day of rivastigmine, cognitive ability, global assessment, and ADLs improved. At lower dosages of 1 to 4 mg/day, the effect was significant only for cognitive ability and global assessment. There are no double-blind placebo-controlled studies of rivastigmine beyond 26 weeks in duration.

Clinical Use

Gastrointestinal side effects appear to limit use of higher doses of rivastigmine by mouth. However, the transdermal formulation appears to be better tolerated among all cholinesterase inhibitors. A 9.5-mg rivastigmine transdermal formulation delivers 9.5 mg over 24 hours, and efficacy is equivalent to the 12-mg/day capsule. The transdermal patch is better tolerated, with 51% of patients reporting at least one adverse event compared to 63% in patients treated with capsules (Cummings, Farlow, Meng, Tekin, & Olin, 2010), suggesting greater clinical value of the transdermal formulation in those more vulnerable to gastrointestinal adverse effects. Further, the pharmacological profile may allow for a higher margin of safety with less potential for drug–drug interactions compared to other cholinesterase inhibitors (Inglis, 2002) (Table 26.5).

Galantamine

Pivotal Trials and Key Findings

Four pivotal trials were included in the FDA's assessment of galantamine in AD. Almost 2,000 patients with mild to moderate AD were enrolled in these randomized, double-blind, placebo-controlled studies (Raskind, Peskind, Wessel, & Yuan, 2000; Tariot et al., 2000; Wilcock, Lilienfeld, & Gaens, 2000; Wilkinson & Murray, 2001). Three trials used fixed galantamine doses and one trial had flexible dosing. Overall, doses ranged between 8 and 32 mg/day, and studies lasted 3 to 6 months. ADAS-cog and CIBIC-plus were primary efficacy measures for three of the trials; ADAS-cog was used in the flexible-dose study (Wilkinson & Murray, 2001).

A small but statistically significant improvement in cognitive function and global change was demonstrated for the groups receiving at least 16 mg/day,

TABLE 26.5 Rivastigmine

Pharmacology	Noncompetitive, slowly reversible cholinesterase inhibitor with inhibition of both acetylcholinesterase and butyryl cholinesterase. Metabolism bypasses the hepatic cytochrome P450 system, incurring a lower risk of drug–drug interactions.
Usual dosing	Rivastigmine 6–12 mg/day in twice-daily dosing
Dosage forms available	Rivastigmine: 1.5-, 3-, 4.5-, 6-mg capsule. Exelon: 1.5-, 3-, 4.5-, 6-mg capsule; 2-mg/mL solution. Rivastigmine transdermal/Exelon patch: 4.6, 9.5, 13.3 mg/24 hours.
FDA-approved indications	Capsule formulation: mild to moderate AD, and mild to moderate dementia associated with Parkinson's disease Transdermal formulation: mild, moderate, and severe AD, and mild to moderate Parkinson's disease dementia
Adverse effects	Nausea and vomiting were reported in the pivotal trials but were less common with slower titration and with food administration (Inglis, 2002). Transdermal formulation: application-site redness or rash, falls, insomnia, vomiting, diarrhea, weight loss, and nausea. These reactions occurred more frequently with the higher-dose Exelon patch (13.3 mg/24 hours) than with the lower-does one (4.6 mg/24 hours). More reports of tremor were noted in the rivastigmine-treated group in patients with Parkinson's disease dementia.

but not for the groups receiving less than 16 mg/day (Tariot et al., 2000). Greater effect was observed in those with an MMSE score of less than 18 (Wilcock et al., 2000). One trial included a 6-month open-label extension and suggested that cognitive improvement was maintained (Raskind et al., 2000). Rates of study withdrawal due to adverse effects were much higher in the 32-mg/day group, and the rapid dose titration over 1 to 2 weeks probably contributed to this (Wilkinson & Murray, 2001).

Meta-analyses and Recent Updates

The SERAD study (Safety and Efficacy of Galantamine in Severe Alzheimer's Disease) examined 407 nursing home residents in Europe with severe dementia over 6 months. Advantage over placebo was demonstrated in the domain of cognitive ability as detected on the SIB but not on ADLs (Burns et al., 2009).

The 2006 revised Cochrane review examined data from 10 clinical trials studying galantamine versus placebo in 6,805 patients with mild to moderate Alzheimer's dementia. Treatment with galantamine at doses of 16 to 36 mg/day, but not 8 mg/day, correlated with improved or unchanged global rating scale scores. At all dosing levels, there was a reduction in the ADAS-cog score and benefit was greater with 6 months of treatment compared to 3 months. The 16-mg/day dosage was best tolerated when titrated over 4 weeks, and efficacy was not statistically greater at dosages of more than 16 mg/day. Extended-release galantamine (16 to 24 mg/day) was found to have similar efficacy and adverse side effect profiles as the equivalent twice-daily regimen (Loy & Schneider, 2006).

Clinical Use

Galantamine was the first cholinesterase inhibitor to be available in generic form in the United States (Table 26.6). Efficacy of the once-daily dosing formulation appears comparable to the twice-daily formulation. The literature supports usual effective dosages of 16 to 24 mg/day. Galantamine's unique pharmacological mechanism—enhancing the response of nicotinic receptors to acetylcholine—while conceptually attractive has not translated into great clinical effectiveness than other cholinesterase inhibitors.

Memantine

Pivotal Trials and Key Findings

Two pivotal trials contributed to memantine's 2003 FDA approval for treatment of moderate to severe AD (Table 26.7). In the first trial, 252 patients with moderate to severe AD in the United States were randomized to receive either placebo or memantine 20 mg/day for 28 weeks. Primary efficacy variables were the CIBIC-plus and ADCS-ADL inventory modified for

TABLE 26.6 Galantamine

Pharmacology	Competitive, reversible inhibitor of acetylcholinesterase, with little butyryl cholinesterase activity, and nicotinic receptor agonism
Usual dosing/routes of administration	Galantamine 16–24 mg/day in twice-daily dosing. Galantamine's prolonged-release formulation is dosed once daily and has similar efficacy and tolerability at comparable doses to the immediate release.
Dosage forms available	Galantamine: 4-, 8-, 12-mg tablets; 8-, 16-, 24-mg extended-release capsules; 4 mg/mL solution. Razadyne: 4-, 8-, 12-mg tablets; 8-, 16-, 24-mg extended-release capsules; 4 mg/mL solution.
FDA-approved indications	Mild to moderate AD
Adverse effects	Nausea, vomiting, diarrhea, weight loss, decreased appetite, dizziness

severe dementia. The memantine group performed better than the placebo group on functional and global outcome measures. There was also improved cognition on the SIB, a secondary outcome measure. Most adverse events were mild to moderate in severity and were judged either not related to or unlikely to be related to memantine (Reisberg et al., 2003).

The second pivotal trial involved combination therapy with stable donepezil treatment. Four hundred four patients taking donepezil for moderate to severe AD received add-on memantine titrated up to 20 mg/day or placebo for 24 weeks. Primary outcome measures were the SIB and ADCS-ADL. Improvements in the memantine group were observed in the domains of cognition and functioning. Only as secondary outcomes were improvements detected in global and behavioral domains (Tariot et al., 2004).

Meta-analyses and Recent Updates

A Cochrane review summarized the findings of 12 randomized trials of memantine in people with AD, vascular, mixed, or unspecified dementia of all degrees of severity (McShane, Areosa Sastre, & Minakaran, 2006). A beneficial effect at 6 months was detected in the moderate to severe AD group treated with memantine in the domains of cognition (2.97 points on the 100-point SIB), activities of daily living (1.27 points on the 54-point ADCS-ADL), behavior (2.76 points on the 144-point NPI), and clinical impression of change (0.28 points on the 7-point CIBIC).

In the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO) study, combination donepezil and memantine treatment was not significantly better than donepezil treatment alone (Howard et al., 2012). After at least 3 months of donepezil treatment, patients with moderate to severe AD were randomized to (a) continue donepezil alone, (b) discontinue donepezil and receive placebo memantine, (c) discontinue donepezil and initiate memantine, or (d) continue donepezil and initiate memantine. Donepezil and memantine individually performed better than placebo but did not differ significantly in the presence or absence of the other.

A prospective, randomized, double-blind, placebo-controlled study did not find any significant treatment benefit of memantine at the 24-week endpoint in moderate to severe AD. However, a significant effect was detected on cognitive and global outcome measures at intermediate time points, weeks 12 and 18 (van Dyck, Tariot, Meyers, & Resnick, 2007).

TABLE 26.7 Memantine

Pharmacology	N-methyl-D-aspartate (NMDA) receptor antagonist that reduces glutamate-induced excitotoxicity; renally cleared
Usual dosing	Memantine 20 mg/day in twice-daily dosing
Dosage forms available	Memantine: 5-, 10-mg tablets; 2 mg/mL solution. Namenda: 5-, 10-mg tablets; 2 mg/mL solution. Namenda extended-release, 28 mg once daily.
FDA-approved indications	Moderate to severe AD
Adverse effects	Headache, diarrhea, dizziness, confusion, hypertension

A meta-analysis reviewed three clinical trials of memantine for mild AD with an MMSE score between 10 and 23. None demonstrated efficacy of memantine for mild AD on primary outcome measures (Schneider, Dagerman, Higgins, & McShane, 2011).

Clinical Use

Memantine is the only medication without a mechanism involving cholinesterase inhibition that is FDA indicated for dementia treatment. Renal metabolism of memantine may confer an advantage when prescribing to patients taking multiple hepatic-metabolized medications. Memantine dose is reduced among those with significant renal insufficiency. As of yet, there are no trials comparing efficacy or tolerability between the conventional immediate-release and the extended-release formulation (Grossberg et al., 2013).

Comparisons Among Treatments

The only randomized double-blind study comparing two cholinesterase inhibitors, donepezil and rivastigmine (tablets by mouth), included 998 individuals with moderate dementia. There was no difference in cognitive or behavioral efficacy outcomes between treatment groups. The rivastigmine group performed better on ADLs than the donepezil group, although higher discontinuation rates may have confounded this analysis. After 16 weeks of treatment, the rivastigmine group had more gastrointestinal adverse events and more discontinuations compared to the donepezil group. However, discontinuation rates were the same for both groups during the 20-month maintenance period (Bullock et al., 2005).

A meta-analysis of 10 clinical trials involving cholinesterase inhibitors was conducted (Birks, 2006). These trials included 4,406 participants with mild, moderate, or severe dementia due to AD and lasted at least 6 months. Patients were treated with donepezil, rivastigmine, or galantamine at the usual recommended dose compared with placebo or another cholinesterase inhibitor. The groups showed benefit on global assessments, cognition, ADLs, and behavioral disturbance. Effect size were not large and even less so for severe AD. There was no difference among cholinesterase inhibitors on efficacy measures.

Treatment Combinations

Studies investigating the effectiveness of the combination of cholinesterase inhibitors and memantine have led to mixed conclusions. Modestly beneficial effects of the addition of memantine treatment to donepezil treatment in moderate to severe AD were described previously. In contrast, two randomized controlled trials found no advantage to combination therapy compared to monotherapy. In 2008, 433 patients with mild to moderate AD already receiving stable cholinesterase inhibitor medication received additional placebo or memantine. At 24 weeks, there was no significant differences in primary or secondary outcome measures, leading to the conclusion that the combination of memantine and donepezil did not show an advantage or any significant differences in tolerability and safety compared to donepezil alone (Porsteinsson, Grossberg, Mintzer, & Olin, 2008).

After discontinuing donepezil or galantamine due to ineffectiveness, 202 patients with moderate to severe AD received rivastigmine 3 to 12mg/day for 16 weeks in an open-label, multicenter study. Nonresponders at week 16 then received memantine as an add-on for 12 additional weeks. At week 28, 78% of patients receiving the combination of rivastigmine and memantine demonstrated improvement on the MMSE, with a mean change from baseline of 1.2 points (Dantoine et al., 2006).

Cholinesterase Inhibitors and Memantine for Dementia Syndromes Other than Alzheimer's Disease

Use of cholinesterase inhibitors in vascular dementia and Lewy body dementia is controversial, although there is supportive evidence. Patients diagnosed with either probable vascular dementia or AD combined with cerebrovascular disease were randomized in a double-blind 6-month trial to receive either galantamine or placebo. Greater efficacy on the primary outcomes, cognition and global function, was demonstrated in the galantamine group, but the study was not powered to compare among the subgroups with AD and cerebrovascular disease or vascular dementia (Erkinjuntti et al., 2002).

In a European trial, 120 patients with Lewy body dementia were randomized to receive either placebo or rivastigmine for 20 weeks. For this multicenter,

double-blind, placebo-controlled study, the NPI agitation subscale and a computerized cognitive assessment system were the primary efficacy measures. Significant improvements in the rivastigmine group were detected on both measures compared to placebo (McKeith et al., 2000). However, neither cholinesterase inhibitors nor memantine are approved in the United States for use in patients with vascular dementia or Lewy body dementia.

Studies that investigate the use of cholinesterase inhibitors in mild cognitive impairment, considered to be prodromal AD in some people, have not shown consistent benefit. Of the nine studies evaluated in a systematic review, only donepezil in one study demonstrated improvement in cognition as the primary outcome measure compared to placebo. The difference in ADAS-cog was small but significant, although other studies did not show benefit on primary outcomes (Cooper, Li, Lyketsos, & Livingston, 2013; Doody et al., 2009).

OTHER TREATMENTS FOR ALZHEIMER'S DISEASE

Natural products and supplements are increasingly popular among the aging population (Barnes, Bloom, Nahin, & Statistics, 2008). The more commonly mentioned include omega-3 fatty acids, s-adenosyl methionine, ginkgo biloba, huperzine A, and vitamin B. While some studies of omega-3 fatty acids and ginkgo biloba suggest neuroprotective properties with a delay in dementia onset, no study has consistently demonstrated treatment efficacy in those with a dementia syndrome (DeKosky et al., 2008; Issa et al., 2006; Lavretsky, 2009; Varteresian, Merrill, & Lavretsky, 2013).

TREATMENT OF NEUROPSYCHIATRIC SYMPTOMS ASSOCIATED WITH ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

Neuropsychiatric symptoms include apathy, depression, irritability, agitation/aggression, and psychosis. These symptoms are now thought to be fundamental expressions of the neurodegenerative process and are considered core clinical features of AD. Over the entire course of AD, 80% to 100% of patients will develop such symptoms. At any given time, more than half of dementia patients will experience behavioral disturbances that can have a negative impact on the quality of life and the health of both patient and caregiver (Lyketsos et al., 2000).

A longitudinal study found that apathy, depression, and agitation were the most commonly reported neuropsychiatric symptoms in dementia and MCI (Lyketsos et al, 2002).The prevalence of overall neuropsychiatric symptoms increases and the symptom profile changes with disease progression. Apathy, depression, anxiety, and irritability are more common in mild AD, and agitation/aggression, delusions, hallucinations, and disinhibition are more common in more advanced stages. Management of neuropsychiatric symptoms is a major priority in dementia care. They are associated not only with impaired quality of life, but also with increased morbidity, caregiver burden, health economic costs, hospitalizations, and nursing home placement.

Improved understanding of the neurobiological etiology of neuropsychiatric symptoms will help guide future treatment developments. Researchers have identified dysfunction in three neurobiological models that may contribute to neuropsychiatric symptoms in AD: frontal-subcortical circuits, cortico-cortical networks, and the monoaminergic system (Geda et al., 2013). Moreover, individual symptoms are related to dysfunction in distinct neural systems (Sultzer et al., 2011, 2013). Further illumination of these models with neuroimaging, regional neuropathology, genetic, and other biomarker studies will inform treatment advances.

Rating scales commonly used to measure neuropsychiatric symptoms in research studies include the following:

- NPI: assesses the frequency and severity of 12 psychiatric and behavioral disturbances in dementia patients, including agitation, psychosis, and mood disturbance
- Neurobehavioral Rating Scale (NRS): a 28-item observer-rated scale with caregiver input. Includes domains of cognition, agitation/disinhibition, behavioral retardation, anxiety/depression, psychosis, and verbal output disturbance.
- Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD): a 25-item scale that includes seven groups of behavior: paranoid/delusional ideation, aggressiveness,

hallucinations, activity, diurnal rhythm, affective symptoms, anxiety, and phobias
- Brief Psychiatric Rating Scale (BPRS): an 18-item clinician-rated scale that measures psychiatric symptoms, including mood, psychosis, anxiety, and motor symptoms
- Cornell Scale for Depression in Dementia (CSDD): developed to assess depression in patients with dementia, based on semistructured interviews with the patient and caregiver
- Cohen-Mansfield Agitation Inventory (CMAI): a 29-item, informant-rated instrument. Categories of agitated behaviors include physical aggression, physical nonaggression (e.g., intense pacing, restlessness, repetitious behaviors), and verbal agitation.

Nonpharmacological Treatments

Behavioral disturbances should first be managed nonpharmacologically whenever possible. A thorough medication review and screen for substance use, including caffeine, can also identify inadvertent psychotropic agents that may exacerbate neuropsychiatric symptoms. Medical conditions such as pain, dehydration, urinary retention, and delirium can contribute to behavioral disturbance and warrant attention. Finally, environmental circumstances that foster neuropsychiatric symptoms or disruptive behaviors are also addressed.

Overall, nonpharmacological interventions are directed toward the patient, the caregivers, and the environment. Nonpharmacological interventions have been grouped into eight categories: sensory interventions, structural activities, social contact, medical/nursing interventions, environmental interventions, behavior therapy, staff training, and combination therapies (Cohen-Mansfield, 2013).

A comprehensive review of nonpharmacological interventions for behavioral symptoms of dementia included various forms of cognitive/emotion-oriented interventions, sensory stimulation interventions, and behavior management techniques (O'Neil et al., 2011). In most studies, there was insufficient evidence to recommend a standardized practice. Although some were randomized controlled trials, the majority of studies were small and methods were inconsistent across trials. The review suggested a beneficial role for sensory stimulations interventions (e.g., light therapy, aromatherapy, and massage/touch therapy) and behavior management techniques (including cognitive-behavioral therapy, token economies, habit training, communication training, and reinforcement strategies). The authors emphasized the need to tailor psychosocial therapies to the individual and to modify the intervention to best suit the caregivers and environment.

A systematic review evaluated 162 studies that used a psychological or psychosocial approach to treating neuropsychiatric symptoms of dementia (Livingston, Johnston, Katona, Paton, & Lyketsos, 2005). Three strategies were best supported by the reviewed literature. Behavioral management techniques tailored to a specific behavior were effective in reducing neuropsychiatric symptoms, and the benefit was sustained for several months. Individualized psychoeducation to change caregivers' interaction with the patient also had lasting effect. Finally, cognitive stimulation in the form of music and sensory enhancement was effective but not long-lasting. The authors noted that while some interventions may not have a substantial impact on neuropsychiatric symptoms, they can provide pleasure to the patient and/or caregiver and thus have value.

Few studies have assessed the effects of combined behavioral and medication treatment or have compared the effects of behavioral and pharmacological interventions. In one study, AD patients with agitated behaviors were treated with either haloperidol (mean dose = 1.8 mg/day), trazodone (mean dose = 200 mg/day), behavioral management techniques, or placebo. Interestingly, there was no significant difference among the groups on the primary outcome measure. Fewer adverse events were reported in the behavioral management group (Teri et al., 2000). These findings may highlight the challenge of matching an optimal treatment to an individual patient or symptom and are consistent with the relatively high placebo response rates seen across studies of the treatment of neuropsychiatric symptoms.

Pharmacological Treatments

To date, no pharmacological interventions are FDA approved for neuropsychiatric symptoms in the United States. In general, providers identify the target symptoms and match them to the relevant

medication class for treatment. However, there is little evidence to support this practice. Improved understanding of neurobiological and other factors that influence the expression of neuropsychiatric symptoms will help to identify the symptoms and the patients most likely to benefit from specific treatments and can provide targets for future treatment development. In many studies of dementia treatments, behavioral outcomes were secondary measures and trial participants had few behavioral symptoms at baseline (Rodda, Morgan, & Walker, 2009). The United Kingdom's Alzheimer's Society has provided clinicians with online practice guidelines (http://alzheimers.org.uk/bpsdguide). Below, we highlight studies that target the most common dementia-associated symptoms: apathy, depression, and agitation/psychosis.

Apathy

Apathy is one of the most frequent behavioral symptoms in AD (Aalten et al., 2007; Robert et al., 2005). The prevalence of apathy is between 55% and 80% in AD (van Reekum, Stuss, & Ostrander, 2005), up to 70% in mixed-type dementia (Mulin et al., 2011), and 56% in Parkinson's disease dementia (Dujardin et al., 2007). Standardized diagnostic criteria for apathy were proposed by Robert and colleagues (2009). Apathy is defined as a disorder of motivation that persists over time and meets the following requirements: (1) the core feature of apathy/diminished motivation must be present for at least 4 weeks; (2) two of the three dimensions of apathy (reduced goal-directed behavior, goal-directed cognitive activity, and emotional reactivity) must be present; (3) symptoms cause clinically significant functional impairment; and (4) symptoms are not due to other states that mimic apathy.

The Apathy in Dementia Methylphenidate Trial (ADMET) was a 6-week, randomized, double-blind, placebo-controlled study that included 60 patients with AD who were treated with either methylphenidate 20 mg/day or placebo. Primary outcome measures were scores on the Apathy Evaluation Scale and modified ADCS CGI-Change. Statistically significant improvement was detected on the ADCS CGI-Change and NPI apathy item score, the latter being a secondary measure. Improvement on the Apathy Evaluation Scale was not statistically significant. The methylphenidate group reported more adverse events of anxiety and weight loss (Rosenberg et al., 2013). Additional methylphenidate studies are in development.

Some studies of cholinesterase inhibitor medication have shown beneficial effects on apathy. In a subanalysis of a placebo-controlled trial of donepezil for moderate to severe AD, the change from baseline on the NPI apathy item was greater in the donepezil group than the placebo group. Moreover, among the 67% of participants with apathy at baseline, apathy scores improved with donepezil treatment, along with anxiety and irritability/lability scores (Gauthier et al., 2002).

Modafanil is a norepinephrine agonist that can increase dopamine and histamine levels in the brain and enhance motor activity. Small studies suggest that modafanil may reduce apathy in AD (Frakey, Salloway, Buelow, & Malloy, 2012). However, the available evidence is not robust enough to endorse routine use.

Depression

Depression in AD is likely different from mood disorders in young adults and in nondemented older adults. Amotivation and psychosis are more common in depression in AD, while guilt, suicidal thoughts, and low self-esteem are less common (Olin, Katz, Meyers, Schneider, & Lebowitz, 2002; Rosenberg et al., 2005). Diagnostic criteria for depression in AD have been developed (Olin et al., 2002). Depending on the population selected and the measure used to define depression, the prevalence of depression in AD ranges between 5% and 40%. Depression in AD is associated with poor quality of life, increased caregiver burden, higher rates of institutionalization, greater functional decline, greater likelihood of physical aggression, and higher rates of mortality (Lyketsos et al., 2003). As a distinct syndrome, depression in AD may respond to antidepressant treatment differently than in young adults or nondemented older adults.

The Depression in Alzheimer's Disease Study 2 (DIADS-2) was a randomized, double-blind, placebo-controlled study that examined the use of sertraline for the treatment of depression in patients with AD (Rosenberg et al., 2010). Participants met Rosenberg's 2005 criteria for depression in AD, which was an advantage over prior depression studies that did not include a dementia-relevant diagnosis. The

primary outcome measure was change in the mood domain on the modified ADCS-CGI-Severity at 12 weeks and secondary outcome measures were change in CSDD and remission. After 12 and 24 weeks of treatment, sertraline was not associated with significant improvement but was associated with a higher incidence of adverse effects. Notably, the majority of patients did demonstrate some improvement, which could have been due to the psychosocial intervention provided to both sertraline and placebo groups. Alternatively, improvement in both groups may have reflected spontaneous improvement of symptoms (Weintraub et al., 2010). A retrospective analysis of the DIADS-2 study found that sertraline was no more efficacious than placebo in subgroups that met diagnostic criteria for major depressive episode, minor depressive episode, or Alzheimer's-associated affective disorder (Drye et al., 2011).

A systematic review and meta-analysis examined antidepressant use for depression in dementia. Seven trials met selection criteria and included 330 patients. Depression measures, depression severity, and study design varied considerably across the trials. Two studies found antidepressants effective (clomipramine, sertraline) while the other five did not (Nelson & Devanand, 2011).

Agitation/Psychosis

Agitation occurs in 20% to 70% of patients with AD and is associated with poor quality of life, increased caregiver burden, and higher rates of institutionalization (Okura et al., 2010). Psychosis, in the form of delusions and hallucination, occurs in 30% to 50% of AD patients and is more prevalent in advanced AD (Craig, Mirakhur, Hart, McIlroy, & Passmore, 2005). Neuroimaging studies suggest that aggressive agitation in AD is associated with dysfunction in distinct fronto-temporal cortical systems (Sultzer et al., 2011). The term "agitation" can include a wide range of behaviors, and variability in the results of treatment studies is at least partly related to variability in the definitions and criteria used to define agitation. A standardized criterion for the syndrome of agitation in cognitive impairment is in development.

Historically, antipsychotic medications were used to treat psychosis, agitation/aggression, and some other neuropsychiatric symptoms in AD, although the evidence base supporting efficacy was thin. More recently concern about the safety and overuse of antipsychotics, particularly in nursing homes, has led to reduced numbers of prescriptions.

Cholinesterase Inhibitors

Compared to placebo, cholinesterase inhibitors may reduce the emergence of neuropsychiatric symptoms over 6-month treatment periods but do not clearly benefit those with active symptoms (Trinh, Hoblyn, Mohanty, & Yaffe, 2003). Studies that suggest that donepezil has efficacy for neuropsychiatric symptoms tend to include patients with no or mild symptoms, to address behavioral outcomes as secondary measures, or to demonstrate benefits that are more apparent for mood symptoms than for agitation or aggression.

In one study that enrolled only patients with clinically significant agitation, 272 AD patients with mean MMSE 8.2, mostly in residential care settings, were randomized to 12 weeks of treatment with either donepezil or placebo (CALM-AD). There was no significant difference in change of agitation symptoms or percent responders between the donepezil and placebo groups, as detected on the CMAI or NPI (Howard et al., 2007).

Improvement in agitation/aggression among patients treated with cholinesterase inhibitors was detected in a secondary analysis of data from a nursing home study. Two hundred eighty nursing home patients with AD were randomized to receive donepezil or placebo treatment. At baseline, agitation/aggression was the most common behavioral symptom among all patients. There was no significant difference between the treatment groups on either NPI-NH total or agitation item scores from baseline to endpoint. However, in a secondary analysis of categorical change, 67% of patients in the donepezil group exhibited significant improvement in agitation/aggression compared to 46% of patients in the placebo group (Tariot et al., 2001).

Memantine

Several studies have indicated that memantine treatment in moderate to severe AD may reduce the emergence of neuropsychiatric symptoms, but evidence supporting efficacy in those with active symptoms is limited. A study of donepezil and memantine suggested that the combination may decrease preexisting

behavioral disturbances and also delay the emergence of new behavioral disturbance in dementia (Cummings, Schneider, Tariot, & Graham, 2006). Significant differences were detected in the agitation, irritability, and appetite domains. However, at baseline the patients demonstrated only mild behavioral symptoms, and the findings emerged from a post hoc analysis of secondary outcomes.

In the DOMINO trial, patients with moderate to severe AD stable on donepezil treatment were randomized to continue donepezil, discontinue donepezil, discontinue donepezil and add memantine, or continue donepezil with memantine added for 52 weeks (Howard et al., 2012). A secondary analysis of total NPI scores (reflecting the sum of all neuropsychiatric symptoms) showed a small but significant benefit of memantine treatment over placebo, regardless of whether the memantine treatment was co-treatment with donepezil or stand-alone treatment. Presence of NPS was not a criterion for inclusion, and results for individual symptoms such as agitation were not reported.

A placebo-controlled trial of memantine in AD patients, specifically with agitated behaviors, showed contrasting results. Patients with AD and clinically significant agitation were randomized to receive either placebo or memantine treatment. No significant difference between groups was apparent on the primary outcome measure of agitated/aggressive behaviors, the CMAI. However, some benefit of memantine treatment was noted on the total NPI score, which was a secondary measure and more broadly encompasses aggregate neuropsychiatric symptoms (Fox et al., 2012).

Antipsychotic Medications

Off-label use of antipsychotic medications continues to be considered a reasonable pharmacological intervention for some patients with dementia and behavioral disturbance, when symptoms are severe and behavioral interventions are not effective (Alexopoulos, Streim, Carpenter, & Docherty, 2004). No medication is approved by the FDA for the treatment of neuropsychiatric symptoms in AD. Risperidone is approved by the European Medicines Agency for short-term treatment of persistent aggression in moderate to severe AD when there is risk of harm and unresponsiveness to nonpharmacological interventions.

The evidence from controlled trials of atypical antipsychotic medications reveals a statistically significant benefit of antipsychotic treatment for agitation/aggression in AD, although the magnitude of benefit is small on average. A large systematic review and meta-analysis assessed 18 placebo-controlled trials of antipsychotic medication for agitation or psychosis in dementia. Small but statistically significant benefits were observed for risperidone and aripiprazole (Schneider et al., 2006). Benefits were not seen in all treatment trials. In a more recent meta-analysis, 14 placebo-controlled trials were evaluated. Small but statistically significant effects were observed for risperidone, aripiprazole, and olanzapine for treatment of psychosis, agitation, and global behavioral symptoms in dementia (Maher et al., 2011). In these trials, the effect size for improvement in psychosis is smaller than for agitation, suggesting that psychosis in dementia is paradoxically a poor prognostic factor for antipsychotic treatment. Efficacy of low-dose quetiapine for agitation or psychosis in AD is not apparent in the controlled trials. Three trials compared effectiveness between risperidone and olanzapine, or risperidone and quetiapine. No significant differences were apparent in psychosis or global outcome (Maglione et al., 2011).

A black box warning was issued by the FDA in 2005 based on pooled results of controlled trials that showed increased mortality risk among dementia patients taking second-generation (atypical) antipsychotic medication. More recent studies support the elevated long-term risk of mortality (Ballard et al., 2009). The extent of risk varies across studies, and some analyses do not show increased mortality risk. Understanding true risk, however, is complicated when the frequency of events is low and the sample size is limited.

Most trials reported adverse effects such as somnolence, falls, injury, syncope, extrapyramidal effects, bruising, edema, and urinary tract infections. Although adverse metabolic changes are usually associated with younger patients, clinically significant weight gain and HDL reduction has been observed with second-generation antipsychotic treatment in dementia patients (Zheng et al., 2009). Further, simultaneous use of psychotropic medication with donepezil may negate the potential cognitive improvement afforded by dementia medication (Holmes et al., 2004; Vigen et al., 2011). When considering antipsychotic treatment in practice, clinicians must weigh the value

of modest benefit against the individual patient's risk for adverse effects and their consequences.

One study of antipsychotic treatment for agitation or psychosis in AD was designed to assess the effectiveness of treatment. The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study was a 42-site, double-blind, placebo-controlled trial that included 421 outpatients with AD and psychosis, aggression, or agitation. Each was initially randomly assigned to receive flexible dosing of olanzapine (mean dose = 5.5 mg/day), quetiapine (mean dose = 56.5 mg/day), risperidone (mean dose = 1.0 mg/day), or placebo, and patients were followed for up to 36 weeks. At any time after 2 weeks of treatment the initially assigned medication could be switched to an alternative treatment because of insufficient efficacy, adverse effects, or other reasons, based on the clinical impression of the blinded treating clinician. Time to discontinuation for any reason, the primary outcome, was no different between the antipsychotic and placebo treatment groups (Schneider et al., 2006). An analysis of clinical symptoms found that at the last observation on the initially assigned drug, those treated with olanzapine or risperidone had improved more than those treated with placebo on global NPS measures (Sultzer et al., 2008). The magnitude of improvement was greatest on the BPRS hostile suspiciousness factor, a measure of anger, aggression, and paranoia. On the BPRS psychosis factor, only risperidone showed benefit compared to placebo. Compared to placebo, antipsychotic treatment groups did not improve in daily functioning, care needs, or quality of life. These findings should be cautiously interpreted given the limitations of the study, including that the study design permitted clinicians to change medications. While this reflects real-world clinical care, the results at least partly reflect clinicians' expectations and behaviors along with medication effects.

One recent study assessed the consequences of discontinuing antipsychotic treatment among AD patients with psychosis or agitated/aggressive behavior who had clearly responded to the treatment. In this study, patients with AD with psychosis or agitation/aggression received open-label flexible-dose risperidone for 16 weeks. Those patients who responded to treatment were then randomized to receive either continued risperidone or placebo for an additional 16-week period, under blinded conditions. Among those switched to placebo treatment, the time to relapse was shorter and the rate of relapse was twice that of those continued on risperidone (60% vs. 33%) (Devanand et al., 2012).

Antidepressants

Sertraline, fluoxetine, citalopram, and trazodone have been evaluated in treatment studies for psychosis or agitation in dementia. Among five placebo-controlled randomized trials, only citalopram demonstrated efficacy for agitation and psychosis (Sink, Holden, & Yaffe, 2005). A recent systematic review identified 19 randomized controlled trials that used antidepressant medication for neuropsychiatric symptoms in dementia. Fifteen studied selective serotonin reuptake inhibitors, including sertraline, citalopram, paroxetine, fluoxetine, and fluoxamine, and the other four studied trazodone. Of these 19 studies, 11 demonstrated some therapeutic benefit for symptoms of irritability, depression, and agitation, although there was no consistent pattern of therapeutic response in any particular category. Not all studies were placebo-controlled and not all patients were diagnosed with Alzheimer's-type dementia (Henry, Williamson, & Tampi, 2011).

Effects of citalopram have been evaluated more recently. In the second phase of the CATIE-AD study, AD outpatients with psychosis or agitation/aggression were randomized to receive olanzapine, risperidone, quetiapine, or citalopram. There were modest improvements in symptoms that did not differ between antipsychotics and citalopram. There were more severe adverse effects with olanzapine and risperidone and more gastrointestinal adverse effects with citalopram (Schneider et al., 2009). Finally, a 9-week double-blind placebo-controlled study of citalopram up to 30 mg/day for agitation in patients with AD was recently completed. The Citalopram for Agitation in Alzheimer Disease Study (CitAD, Porsteinsson et al., 2014) randomized 186 patients with probable AD and clinically significant agitation to a psychosocial intervention plus either citalopram or placebo. The primary outcome measures were change in the scores on the NBRS agitation subscale and the modified ADCS-CGIC. Patients who received citalopram had significantly greater improvement on both agitation measures compared to those on placebo. However, patients in the citalopram group experienced worsening cognition and QT interval prolongation compared to the placebo group.

In a randomized, double-blind, parallel-group study, the effects of trazodone and haloperidol were

compared in AD patients with agitation using the CMAI (Sultzer, Gray, Gunay, Berisford, & Mahler, 1997). Overall, the efficacy of the two drugs was comparable, but adverse effects were more common in the haloperidol group. Patients with concomitant mild depressive symptoms exhibited better CMAI response to trazodone than haloperidol (Sultzer, Gray, Gunay, Wheatley, & Mahler, 2001). In contrast, patients with coexisting psychosis, as indicated on the BEHAVE-AD delusions and hallucinations subscores, did not respond better to haloperidol. The extent of improvement in agitated behaviors from trazodone or other serotonergic medications may be mediated by the presence of coexisting mood symptoms. In contrast, another randomized trial that compared trazodone, haloperidol, a behavioral management technique, and placebo for treatment of agitated behaviors in AD showed no difference in efficacy outcomes across the four groups (Teri et al., 2000).

Mood Stabilizers: Valproate and Carbamazepine

Five randomized controlled trials and one meta-analysis assessed the use of valproate for agitation in dementia, and most did not find improvement on global NPS scales (Herrmann, Lanctôt, Rothenburg, & Eryavec, 2006; Porsteinsson et al., 2001; Sival, Haffmans, Jansen, Duursma, & Eikelenboom, 2002; Tariot et al., 2001, 2005). Of the trials, two showed improvement on agitation subscales, although there were methodological limitations (Konovalov, Muralee, & Tampi, 2008). The first placebo-controlled study of valproate for agitation in dementia showed improvement on the BPRS Agitation subscale and the CGI, but the BPRS improvement did not reach statistical significance without second-order analysis, medications were handled by a nonblinded physician, the sample size was small, and the study duration was only 6 weeks (Porsteinsson et al., 2001). A Cochrane review of valproate for neuropsychiatric symptoms in dementia found that adverse effects were more commonly reported in the valproate-treated groups and were often clinically troubling. Those effects included sedation, falls, gastrointestinal upset, urinary tract infection, and thrombocytopenia (Lonergan & Luxenberg, 2009).

Three randomized controlled trials and one meta-analysis evaluated the use of carbamazepine for neuropsychiatric symptoms in dementia. In contrast to findings with valproate, most studies showed evidence of benefit from carbamazepine treatment for agitation in dementia. However, the potential drug–drug interactions from shared CYP450 metabolism and the black box warnings for potentially fatal skin reactions and hematological toxicity limit its use by clinicians. Common adverse effects included diarrhea, sedation, and dizziness, although these were generally mild (Tampi et al., 2011).

Adrenergic Antagonists: Prazosin

Prazosin is an alpha-1 receptor antagonist that may have anxiolytic properties. One study examined its use in patients with AD and agitation. In an 8-week, randomized, placebo-controlled parallel group study, 22 patients with agitation and aggression and probable or possible AD were randomized to receive placebo or prazosin, up to 6 mg/day. The patients treated with prazosin (mean dose = 5.7 mg/day) demonstrated improvement on all three primary outcome measures, the CGIC, NPI, and BPRS (Wang et al., 2009). More evidence would be useful, and a larger study of prazosin by the Alzheimer's Disease Cooperative Study is planned.

LIMITATIONS AND SUMMARY

A large majority of the dementia literature focuses on AD. Because of likely pathophysiological differences, the treatments for AD are not always generalizable to other forms of dementia. However, clinicians still prescribe AD medications for non-AD syndromes because there are relatively few studies available to guide clinicians otherwise. One exception is the understanding that cholinesterase inhibitors may exacerbate behaviors in frontotemporal dementia (Mendez, Shapira, McMurtray, & Licht, 2007).

Only three placebo-controlled trials have provided data beyond 6 months. As a result, there is little evidence guiding clinicians about when to discontinue medications for treatment of dementia or neuropsychiatric symptoms. Also, participants in clinical drug trials may not be representative of patients seen in primary care or specialty care settings. Strict inclusion and exclusion criteria may select for cohorts that favor one treatment domain over another, rendering study results difficult to interpret clinically. Current

treatment options for dementia and neuropsychiatric symptoms associated with dementia are limited, and the evidence to support their efficacy is modest.

TREATMENTS IN DEVELOPMENT FOR ALZHEIMER'S DISEASE

The lack of substantially efficacious treatments for AD and the increasing worldwide prevalence of the disorder have spurred efforts to develop new treatments for AD and, ideally, preventive strategies. Improved understanding of the neurodegenerative process at the molecular level has helped to guide recent treatment approaches.

There have been no new approved treatments for the symptoms of AD since 2004. New treatment efforts are focused on modifying the neurodegenerative process and thereby improving or arresting the course of disease progression. Specific steps in AD pathophysiology have been targeted, including amyloid production, amyloid aggregation, tau phosphorylation, neurofibrillary tangle formation, oxidation and lipid peroxidation, inflammation, and neuronal apoptosis. While such targeted therapies are more likely to be effective, many compounds have unfortunately not demonstrated efficacy in late-phase clinical trials over the past few years. In addition, while disease modification is a key treatment goal, clinical trials to measure treatment effects on disease progression are necessarily extended up to 18 months or beyond, and are thus lengthy and costly.

Several specific approaches have been tested and continue to be explored in clinical trials (Table 26.8). Anti-amyloid approaches include drugs that reduce beta-amyloid production by shifting amyloid precursor processing toward the production of less toxic peptides. Gamma-secretase inhibitors and modulators and beta-secretase inhibitors have advanced to phase 3 testing, but studies to date have not shown significant benefit or have suggested safety concerns. Active or passive anti-amyloid immunization can reduce toxic amyloid burden in the brain. Infusion of specific monoclonal antibodies has been shown to engage the amyloid target in some studies using brain, cerebrospinal fluid, or plasma biomarkers. However, 18-month phase 3 trials of bapineuzemab and solanezumab did not meet primary efficacy outcomes for cognitive improvement in mild to moderate AD, and bapineuzemab treatment was associated with amyloid-related neuroimaging abnormalities due to edema or effusion in approximately 10% of treated individuals (Sperling et al., 2013). A post hoc analysis of the solanezumab trial data revealed improved cognition in the subgroup of AD participants with mild cognitive deficits at baseline (Dean

TABLE 26.8 Targeted Mechanisms in Drug Development for Alzheimer's Disease or Prodromal Alzheimer's, and Examples of Drugs in Development

Mechanism or Treatment Target	*Examples of Drugs in Development*
Gamma- and beta-secretase inhibitors and modulators	Semagacestat Avagacestat LY2886721 MK8931
Immunotherapy, anti-amyloid and others	Bapineuzumab Solanezumab Crenezumab Human immunoglobulin
Amyloid aggregation	Tramiprosate
Tau aggregation	Methylene blue
Antioxidant	Vitamin E Resveratrol
Neuroprotection and other mechanisms	Dimebon (latrepirdine) PPAR agonists (e.g., pioglitazone) Intranasal insulin

Some of the drugs have not shown efficacy or revealed adverse effects in clinical trials and some are no longer in active development. Their underlying mechanisms may continue to be relevant. Other drugs are in ongoing human trials or other phases of development.

et al., 2013), consistent with the hypothesis that inhibiting beta-amyloid before more widespread neuropathology develops or clinical symptoms emerge is key to modifying the course of clinical symptoms. A follow-up study in patients with mild symptoms of AD who also have biomarker evidence of abnormal beta-amyloid is in progress. Trials of several other monoclonal antibodies are ongoing.

Other treatment approaches in development target toxic oxidative stress, inflammation, mitochondrial metabolism, neurotransmitter deficits, synaptic loss, or myelin abnormalities associated with the AD process, or provide homeostatic support via growth factors or stem cells. Some of these approaches are early in development.

Other treatments for AD symptoms that address neurotransmitter or neuroreceptor deficits, inflammation, or oxidative stress are farther along in development, although robust symptomatic improvement has not been demonstrated in most late-phase clinical trials. A recent longer-term study of vitamin E treatment showed modest benefit on measures of functional skills in mild to moderate AD (Dysken et al., 2014). These results, combined with evidence from trials of cholinesterase inhibitors and memantine, indicate that, while beneficial effects are modest on average, addressing neurotransmitter changes and oxidative stress related to AD pathology will continue to have a role in treating AD symptoms for many years, pending the availability of safe and effective disease-modifying treatments.

Two advances are contributing to treatment development for AD. First, animal models in mice and rats bred to express human beta-amyloid pathology can be used to evaluate the sequence of neurodegenerative events in AD disease progression, the relationships between neuropathologies and clinical symptoms, and the effects of interventions that target these pathologies. Second, biomarkers for AD-related biologies in humans can be measured in plasma and cerebrospinal fluid and noninvasively in the brain using neuroimaging techniques. These biomarkers for AD-related neuropathologies provide tools to evaluate drug–target engagement and also the longitudinal impact of treatment on the pathology represented. Biomarkers have been used in phase 3 trials to demonstrate treatment-related clearance of fibrillar amyloid from the brain, using amyloid ligand positron emission tomography (PET) neuroimaging. Such studies will help to refine understanding of key AD treatment mechanisms and can help to identify patients most likely to benefit.

Symptom prevention trials can take advantage of known genetic risk for AD or biomarker evidence of AD pathology before clinical symptoms are present. Three such multiyear treatment studies are in progress. Two trials (Dominantly Inherited Alzheimer Network trial; Alzheimer Prevention Initiative trial) include asymptomatic genetic risk carriers from kindreds with early-onset familial AD. Active treatments in these trials are either monoclonal anti-amyloid antibody or secretase inhibitor. The third trial (A4 trial, Alzheimer's Disease Cooperative Studies) includes older adults without cognitive deficits but with neuroimaging evidence of fibrillar amyloid deposits in the brain. Participants are being treated with anti-amyloid drug or placebo for 3 years and will be assessed longitudinally for the evolution of neurodegeneration markers and cognitive symptoms over time. These trials represent a first step toward the prevention of cognitive, functional, and behavioral symptoms in those at risk for AD.

There are also continued efforts to develop better treatments for neuropsychiatric symptoms such as apathy, depression, psychosis, and agitation/aggression in AD. Improved definitions of the clinical syndromes are in place. Behavioral interventions are being refined and optimal implementation strategies are under investigation. Pharmacological interventions have been broadened to include drugs that target alternative neurotransmitter/neuroreceptor systems, and drug development is increasingly guided by improved understanding of the neurobiological underpinnings of the clinical symptom clusters.

AUTHOR NOTE

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27

Psychological Treatments for Personality Disorders

Paul Crits-Christoph
Jacques P. Barber

A type 2 randomized controlled trial (RCT) found that 20 weeks of cognitive-behavioral therapy (CBT) led to greater improvement than either brief dynamic therapy or a waitlist control for *DSM-IV* avoidant personality disorder. Another type 2 RCT for avoidant personality disorder compared three group-administered behavioral interventions (graded exposure, standard social skills training, intimacy-focused social skills training) with a waitlist control; although all three treatments were more efficacious than the control condition, no differences among the treatments were identified either after the 10-week treatment or at follow-up. For the treatment of borderline personality disorder (BPD), a meta-analysis found statistically significant effects indicating a beneficial effect of dialectical behavior therapy (DBT) over treatment as usual for improvements in anger (two RCTs), parasuicidality (three RCTs), and mental health (two RCTs). All of these effects were moderate to large in size. However, DBT is not uniquely effective for BPD, with two type 1 RCTs finding equal effects for versions of psychodynamic therapy. Another type 1 study found that mentalization-based psychodynamic therapy was superior to structured clinical management in the treatment of BPD in terms of steeper declines in both self-reported and clinically significant problems, including suicide attempts and hospitalization. Single type 1 studies have also supported the efficacy, compared to treatment as usual, of cognitive therapy, schema therapy, and Systems Training for Emotional Predictability and Problem Solving (a therapy that combines cognitive-behavioral techniques and skills training with a systems component) as treatments for BPD. A meta-analysis of five RCTs concluded that there is insufficient trial evidence to justify using any psychological intervention for adults with antisocial personality disorder. No RCTs of psychological treatment for other personality disorders have been reported. Several review articles have found a consistent adverse impact of personality disorders on outcomes of treatment for a wide range of Axis I disorders.

DEFINITION, EPIDEMIOLOGY, AND ETIOLOGY OF PERSONALITY DISORDERS

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013a) defines personality disorders in terms of enduring patterns of thinking about oneself and others that significantly and adversely affect how an individual functions in various aspects of life. The *DSM-5* describes 10 specific personality disorder diagnoses. These are grouped into three clusters: (a) the "odd" cluster (paranoid, schizoid, and schizotypal), (b) the dramatic cluster (histrionic, narcissistic, antisocial, and borderline), and (c) the anxious cluster (avoidant, dependent, obsessive-compulsive). The criteria for diagnosing individual personality disorders

were unchanged between *DSM-IV* and *DSM-5*. Because *DSM-5* has moved to a single-axis system, personality disorders are no longer classified as "Axis II" disorders. An alternative trait-based model of personality disorders was proposed for *DSM-5*, but this alternative model was rejected as too complex for clinical practice (American Psychiatric Association, 2013b). However, a hybrid model that combines elements of the existing criteria for personality disorders with the trait-based approach was included in Section III of *DSM-5* to stimulate further study.

Although personality disorders are relatively common compared with many other psychiatric disorders, estimates of the prevalence of different personality disorders have been hampered by difficulty in reliably assessing these disorders. Strides have been made in the development of structured clinical interviews for assessing personality disorders, but to date these instruments have displayed modest and variable convergence (Clark, Livesley, & Morey, 1997; Perry, 1992; Widiger & Samuel, 2005) among themselves or with other measures. Poor convergent validity in assessing personality disorders suggests that one cannot necessarily treat similarly results from studies that use different instruments, thus limiting the validity of these measures (Perry, 1992). However, advances have been reported in the reliability of these measures. Maffei and colleagues (1997), for example, reported acceptable interrater reliability coefficients of 0.49 to 0.98 (kappas) for *DSM-IV* categorical diagnoses and excellent intraclass correlation coefficients from 0.90 to 0.98 for dimensional judgments. The Collaborative Longitudinal Personality Disorders Study (Zanarini et al., 2000), which focused on schizotypal, borderline, avoidant, and obsessive-compulsive personality disorders, also reported relatively good median interrater reliability kappa coefficients (0.40 to 0.75) for all personality disorders diagnosed five times or more, and excellent reliability for the diagnosis of antisocial personality disorder (kappa = 1.0). This study also found excellent interrater reliability (>0.75) when dimensional scores were used.

International community-based epidemiological studies have put the overall prevalence of *DSM-IV* personality disorders at about 6% for any personality disorder and 3.6%, 1.5%, and 2.7% for clusters A, B, and C, respectively (Huang et al., 2009). In the United States, the prevalence rate for any personality disorder has been estimated at 9.1% (Trull et al., 2010). For individual personality disorders, Trull and colleagues (2010) report the following prevalences: paranoid, 1.9%; schizoid, 0.6%; schizotypal, 0.6%; borderline, 2.7%; histrionic, 0.3%; narcissistic, 1.0%; antisocial, 4.1%; obsessive-compulsive, 1.9%; avoidant, 1.2%; and dependent, 0.3%. The presence/absence of a personality disorder has been found to be stable over 2 years among adolescents in a psychiatric setting (Chanen et al., 2004). However, a study examining stability of personality disorders in adults over a 4-year period found statistically significant variation in personality disorder features over time, suggesting that such features are not always enduring (Lenzenweger, Johnson, & Willet, 2004). The impairment in functioning that is commonly seen in those individuals with personality disorders does appear to be a relatively enduring aspect of these disorders (Skodol et al., 2005).

There is also an extensive amount of comorbidity among personality disorders—that is, having one disorder tends to be associated with having one or more additional personality disorder diagnoses. For example, Zimmerman, Rothschild, and Chelminski (2005) reported that, among psychiatric outpatients, 60.4% of those who had a personality disorder had more than one personality disorder, and 25.2% had two or more. In some disorders, such as BPD, the comorbidity rate ranges from 90% to 97% (Gunderson, Zanarini, & Kisiel, 1991).

Comorbidity of personality disorders with other psychiatric disorders is especially important for treatment planning. Data from the National Comorbidity Survey Replication, a large-scale U.S. epidemiological study, has provided the best evidence regarding such comorbidity. Results indicate that, with respect to antisocial personality disorder, 70.2% of patients with this personality disorder also meet criteria for at least one psychiatric disorder in the previous 12 months, with an average of 3.4 such disorders (Lenzenweger et al., 2007). For BPD, 84.5% of cases also have at least one other 12-month psychiatric disorder. For cluster A as a group, 41.1% have another psychiatric disorder; for cluster C, 49.7% have another disorder. Of those with a (non-personality disorder) psychiatric disorder, 25.2% also have at least one personality disorder (Lenzenweger et al., 2007).

Comorbidity of Axis II with substance use disorders has been studied extensively and has been found to be particularly high. Trull and colleagues (2010) report high comorbidity rates for lifetime alcohol dependence among those with antisocial (49.2%),

histrionic (49.8%), and borderline (47.4%) personality disorders. Comorbidity with lifetime drug dependence was high with histrionic (29.7%), dependent (27.3%), and antisocial (23.4%) personality disorders (Trull et al., 2010).

Little is known about the etiology of personality disorders. A number of studies have documented high rates of physical and sexual abuse or other trauma during childhood in patients later diagnosed as having BPD (Herman, Perry, & van der Kolk, 1989; Ogata, Silk, Goodrich, Lohr, Westen, & Hill, 1990; Westen, Lundolph, Misle, Ruffins, & Block, 1990). Most recently, Waxman and colleagues (2014) found that BPD and schizotypal personality disorder were most strongly predicted by sexual abuse, antisocial personality disorder by physical abuse, and avoidant and schizoid personality disorders by emotional neglect. However, a recent study implicated prenatal adversity (tobacco smoking, drug taking, maternal traumatic stress, medical complications) in the pathogenesis of BPD (Schwarze et al., 2012). Other studies have found evidence for familial transmission of BPD (Baron, Gruen, Asnis, Asnis, & Lord, 1985; Loranger, Oldham, & Tullis, 1982) and schizotypal personality disorder (Baron et al., 1985). Studies have supported a genetic component for schizotypal personality disorder (Torgersen, 1984) and BPD (Distel et al., 2008). Twin research, however, has suggested that the genetic risk factors for *DSM*-IV personality disorders do not reflect the cluster A, B, and C typology (Kendler et al., 2008). Instead, genes convey a broad vulnerability to personality disorder pathology and/or negative emotionality. There is also a rich literature on the childhood precursors (most important, the presence of conduct disorder in childhood and behavioral disinhibition) of antisocial personality disorder (Paris, 2000).

HISTORICAL PERSPECTIVE

Early psychoanalytic writings devoted a considerable amount of attention to the treatment of "characterological" problems (Alexander, 1930; Fenichel, 1945). Although some of this literature informs modern approaches, particularly modern psychodynamic approaches, it is difficult to see the relevance of these early writings to the current classification system for psychiatric disorders. For example, the distinction between obsessive-compulsive disorder and obsessive-compulsive personality disorder was not made in early writings on "obsessive-compulsive" character, and this distinction is likely to be important for treatment selection.

Within the psychodynamic literature, there has been voluminous writing on the nature and treatment of narcissistic and borderline personality types in particular (Kernberg, 1984; Kohut, 1984; see review by Aronson, 1989). Even in these more recent writings, however, there has remained a lack of use of a consensual definition of the target patient population. As a consequence of the varying definitions of "characterological" conditions, the research literature on the treatment of personality disorders begins with the advent of the *DSM-III* and *DSM-III-R* classification system for personality disorders.

This is not to say that the *DSM* definition of personality pathology is not without problems. A number of authors have described various problems with the *DSM* classification, including lack of discrimination of many of the *DSM* criteria (Svrakic & Divac-Jovanovic, 1994), problems in distinguishing normal from deviant personality (Livesly, Schroeder, Jackson, & Jang, 1994), and general lack of empirical support (Widiger, 1993). These problems with the *DSM* system generated the proposed trait-based alternative that is contained within the hybrid model in Section III in *DSM*-5. Further research will determine whether this hybrid model is incorporated into the next edition of the *DSM*.

REVIEW OF TREATMENT OUTCOME LITERATURE

Despite the relatively high prevalence of personality disorders, there have been relatively few outcome studies using patients with these disorders. Since the third edition of *Treatments That Work* (Nathan & Gorman, 2007), additional important research on the treatment of BPD has been published, but there continues to be little attention to other personality disorders.

The first meta-analysis on the effectiveness of psychotherapy for personality disorders in general was published by Perry, Banon, and Ianni (1999). These authors found 15 studies that attempted to systematically diagnose their patients and evaluate outcome. Since most of these studies were not randomized trials, the authors calculated the within-treatment

change effect size, which ranged between 1.1 and 1.3 depending on the measure. In addition, they compared results from four studies that reported the percentage of patients who no longer met Axis II criteria at follow-up with studies that examined the natural history of recovery of BPD patients. They showed that, in comparison to the natural history of the latter, personality disorder patients who received psychotherapy had a sevenfold faster rate of recovery. Unfortunately, only half of the patients in the four studies had a diagnosis of BPD, thus limiting the validity of the comparison.

Another meta-analysis compared psychodynamic therapy (n = 14 studies) and CBT (n = 11 studies) in the treatment of various personality disorders (Leichsenring & Leibing, 2003). Because many of the studies were uncontrolled, the authors relied on within-group effect sizes and concluded that there was evidence that both treatments are effective. However, many of the studies did not standardize treatment, and therefore it is difficult to know what interventions were actually provided. Because of this problem and the lack of controlled comparisons, these results cannot be used to provide empirical support for the use of specific treatment modalities with specific patient disorders or problems. A more recent meta-analysis focused on RCTs of at least moderate quality (eight studies) that investigated psychodynamic therapy for any type of personality disorder (Town, Abbass, & Hardy, 2011). The authors concluded that short-term psychodynamic therapy may be considered an efficacious empirically supported treatment option for a range of personality disorders, with significant and medium- to long-term improvements for a large percentage of patients.

A final recent meta-analysis examined the efficacy of psychodynamic therapy for personality disorders, relying solely on evidence from RCTs (Barber, Muran, McCarthy, & Keefe, 2013). They found that psychodynamic therapy for personality disorder was more effective than treatment as usual or waitlist controls (study n = 7, subject n = 452, g = 0.593, p = 0.001). Psychodynamic therapy also did not differ from alternative therapies for personality disorder (study n = 7, subject n = 528, g = –0.145, p = 0.150).

In the next sections, we summarize the existing literature on the treatment of personality disorders using the type 1 to type 6 classification of studies employed in this volume. Our emphasis is on type 1 and type 2 studies with patients who meet *DSM-III*, *DSM-III-R*, or *DSM-IV* criteria. Type 3 through type 6 studies, including any study using pre–*DSM-III* criteria, are mentioned only when no type 1 or 2 studies are available.

AVOIDANT PERSONALITY DISORDER

An RCT on *DSM-III* avoidant personality disorder compared graded exposure, standard social skills training, intimacy-focused social skills training, and a waitlist control (Alden, 1989). The behavioral treatments were all administered in group format. All of the active treatments were better than the waitlist, but no differences among the behavioral treatments were found at the end of the 10-week treatment period or at follow-up. Examination of the clinical significance of the outcomes revealed that although positive changes had occurred in the active treatment conditions, patients were not functioning at the level of normative comparison samples. This study, however, had minimal statistical power for detecting differences among the treatments (<20 patients per group) and therefore is a type 2 study.

One randomized trial (type 2) compared 20 weeks of brief dynamic therapy (n = 23), CBT (n = 21), and a waitlist control (n = 18) for *DSM-IV* avoidant personality disorder. The results indicated that patients who received CBT showed significantly greater improvement on a number of outcome measures in comparison to both the brief dynamic therapy and the waitlist groups. Results were maintained at follow-up.

One type 3 study (not controlled) has been reported on *DSM-III-R* avoidant personality disorder (Renneberg, Goldstein, Phillips, & Chambless, 1990). This study evaluated an intensive (4 full days) group behavioral treatment program with 17 patients. The treatment included group systematic desensitization, behavioral rehearsal, and self-image work. Outcome was evaluated at posttreatment and 1-year follow-up. The results evidenced positive changes, especially in terms of fear of negative evaluation. Gains were maintained over the follow-up period.

In a comparative study without a control group, Stravynski, Lesage, Marcouiller, and Elie (1989) compared social skills training with group discussion plus homework in a crossover design for patients with *DSM-III* avoidant personality disorder. Although significant improvements on most measures were found in general, no differences between the treatment

modalities were found, questioning the centrality of skills acquisition as the mechanism of action of social skills training. Treatment, however, may have been too brief (five sessions of each modality) to detect an effect. More recently, Stravynski, Belisle, Marcouiller, and Lavallee (1994) examined whether a combination of office-based and in vivo (real-life interactions with people in shopping malls, a cafeteria, and so forth) enhanced the outcome of office-based social skills training for 28 patients with *DSM-III* avoidant personality disorder. Outcomes were generally equal in the two conditions, although the in vivo condition had a greater attrition rate.

Because avoidant personality disorder appeared to be equally responsive to different kinds of behavioral treatments, Alden and Capreol (1993) examined the hypothesis that different kinds of interpersonal problems would moderate treatment response to various therapies. To test this hypothesis, data from the Alden (1989) project described above were used. Several findings emerged. Avoidant personality disorder patients who had greater problems related to distrustful and angry behavior benefited more from structured exercises that required them to approach and talk to others (graded exposure). Patients with problems resisting others' demands benefited from both graded exposure and social skills training but were particularly responsive to intimacy-focused social skills training. The results suggest that a comprehensive assessment of interpersonal problems may be important in planning what type of treatment intervention is most likely to be beneficial to patients with avoidant personality disorder.

In a quantitative case study, Coon (1994) has reported on the successful treatment of avoidant personality disorder using a schema-focused cognitive therapy. Positive outcomes were evidenced not only at termination but also at the 1-year follow-up. Similarly, a quantitative case study of a 5-year psychoanalysis for avoidant personality disorder showed clinically significant reductions in symptom severity and relational pathology at termination, with gains maintained at the 1-year follow-up (Porcerelli et al., 2007).

In an uncontrolled pilot (type 3) study of 52 weeks of supportive-expressive dynamic therapy, Barber, Morse, Krakauer, Chittams, and Crits-Christoph (1997) showed that, by the end of treatment (up to 52 sessions), 61% of carefully diagnosed avoidant personality disorder patients had lost their avoidant personality disorder diagnosis.

OBSESSIVE-COMPULSIVE PERSONALITY DISORDER

Barber and colleagues (1997) conducted an open trial of supportive-expressive dynamic therapy for obsessive-compulsive personality disorder (type 3 study). Obsessive-compulsive personality disorder patients lost their personality disorder diagnoses significantly faster than did avoidant personality disorder patients. By the end of treatment, 39% of avoidant personality disorder patients retained their diagnosis, whereas only 15% of obsessive-compulsive personality disorder patients (1 out of 13) did so. Most obsessive-compulsive personality disorder patients lost their diagnoses within the first 17 sessions of treatment. Both avoidant personality disorder and obsessive-compulsive personality disorder patients improved significantly across time on measures of personality disorders, depression, anxiety, general functioning, and interpersonal problems.

BORDERLINE PERSONALITY DISORDER

The most widely investigated treatment for any personality disorder has been DBT for BPD. DBT is actually a complex treatment modality that is more accurately described as eclectic rather than a traditional behavior therapy per se. The treatment consists of weekly group and individual sessions for a year. The group component includes psychoeducation, teaching interpersonal skills, distress tolerance/reality acceptance, and emotion regulation skills. The individual therapy sessions involve directive, problem-solving techniques, as well as supportive techniques such as empathy and acceptance. Behavioral goals serve as the focus of the individual sessions and are addressed in a sequential order, but previous goals are readdressed if the problem returns. These goals include decreasing suicidal behaviors, decreasing therapy-interfering behaviors, decreasing behaviors that interfere with quality of life, increasing behavioral skills, decreasing behaviors related to posttraumatic stress, increasing respect for self, and achieving individual goals. More details about DBT can be found in the published treatment manual (Linehan, 1993).

A recent Cochrane review (Stoffers et al., 2012) provides a systematic, meta-analytic overview of the literature on psychosocial treatments for BPD. This meta-analysis summarized all available

randomized studies involving samples of patients with BPD that compared a specific psychotherapeutic intervention against a control intervention or against a comparative specific psychotherapeutic intervention. Twenty-eight studies involving a total of 1,804 participants with BPD were included in the review. Calculation of effect sizes averaging over studies could only be done for comparison of DBT to treatment as usual. These included studies by Carter and colleagues (2010), Koons and colleagues (2001), Linehan, Hubert, Suarez, Douglas, and Heard (1991), Linehan and colleagues (2006), and Verheul and colleagues (2003). There were statistically significant effects indicating a beneficial effect of DBT over treatment as usual for improvements in anger (n = 46, two RCTs), parasuicidality (n = 110, three RCTs) and mental health (n = 74, two RCTs). All of these effects were moderate to large in size. However, there was no evidence of superiority of DBT over treatment as usual in terms of keeping participants in treatment (n = 252, five RCTs). All remaining findings reported in the review by Stoffers and colleagues (2012) were based solely on single studies; all of these single studies are reviewed in the following paragraphs.

Whether DBT is uniquely effective for BPD or for suicidal BPD has not been well established. Using opiate-dependent patients with comorbid BPD who were being treated with concurrent opiate agonist therapy, Linehan and colleagues (2002) compared DBT to another psychotherapy treatment (comprehensive validation therapy with 12-step) that consisted of the nonspecific elements of DBT (therapeutic warmth, responsiveness, and empathy) in combination with participation in 12-step programs. On most outcomes, there were no significant differences between the treatment groups, although the sample size was limited (type 2 study). In addition, results of a large RCT (type 1) indicate that, in the treatment of BPD, outcomes for DBT were no better than those for transference-focused psychotherapy or supportive psychotherapy (Clarkin et al., 2007). Another large RCT (type 1) found that DBT and general psychiatric management were not significantly different in the treatment of BPD (McMain et al., 2009). However, a small, randomized (but otherwise naturalistic) study (type 2) found that DBT (n = 12) was superior to client-centered therapy (n = 12) at 12 months on most outcome measures (Turner, 2000).

Nonrandomized (type 3) studies of DBT with special populations have also been reported. In an adaptation of DBT for suicidal adolescents with borderline personality features, DBT was found to yield better treatment retention and fewer hospitalizations than a nonrandomized treatment-as-usual control group (Rathus & Miller, 2002). In another nonrandomized comparison, Evershed and colleagues (2003) reported that DBT was superior to treatment as usual for male forensic patients with BPD in a high-security hospital, especially in reducing the seriousness of violence-related incidents and self-report of anger. Uncontrolled studies reporting favorable outcomes for DBT adapted for patients with eating disorders and BPD (Palmer et al., 2003) and posttraumatic stress disorder and BPD (Lanius & Tuhan, 2003) have also been published.

An intensive (3-week) version of DBT has also been evaluated as crisis intervention for outpatients with BPD. The intensive program appeared to retain patients well and reduced symptoms of depression and hopelessness (McQuillan et al., 2005).

Psychodynamic therapy in various forms has been evaluated in multiple RCTs as a treatment of BPD. In one early study (Stevenson & Meares, 1992; type 3 study), the treatment was, broadly speaking, based on self-psychology. Therapy had a maturational goal accomplished through helping the patient discover and elaborate his or her inner life, with empathy and attention to disruptions in empathy central aspects of the process of therapy (Meares, 1987). Thirty patients with *DSM-III* BPD were treated with twice-per-week therapy for 1 year. Outcome was assessed 1 year after termination of treatment. Substantial reductions in violent behavior, drug use, medical visits, episodes of self-harm, time away from work, and symptoms were found. Thirty percent of patients no longer met criteria for BPD. Improvement was maintained at 1- and 5-year follow-ups, with substantial saving in health care costs (Stevenson & Meares, 1999; Stevenson, Meares, & D'Angelo, 2005).

Munroe-Blum and Marziali (1995) compared open-ended individual psychodynamic therapy with a manualized interpersonal group therapy for 110 patients with BPD (type 1 study). The group treatment lasted 30 sessions. No differences between the groups at 1 year (termination) or 2 years were found, although patients in general benefited from both treatments.

Bateman and Fonagy (1999) reported on the treatment of BPD patients randomized to partial hospitalization (n = 19) or to standard care (n = 19; type 2 study). The partial hospitalization treatment included individual and group psychoanalytic psychotherapy (not standardized) for a maximum of 18 months. In this program, the therapies and informal patient–staff contact were guided by a psychoanalytic model of BPD as a disorder of attachment, separation tolerance, and mentalization (this refers to the capacity to think about oneself in relation to others and to understand others' state of mind). The standard care control condition consisted of regular psychiatric review with a senior psychiatrist and inpatient admission as appropriate with discharge to non-psychoanalytic psychiatric partial hospitalization focusing on problem solving, followed by outpatient and community follow-up (without formal psychotherapy). Results indicated that patients in the partial hospitalization group improved significantly more than controls in terms of decreased number of suicidal attempts, acts of self-harm, psychiatric symptoms, and inpatient days, and better social and interpersonal functioning at 6 months and 18 months (Bateman & Fonagy, 1999, 2001). In a subsequent trial (Bateman & Fonagy, 2009) (type 1), the mentalization treatment was manualized and delivered on an outpatient basis. Patients with BPD were randomized to the mentalization-based psychodynamic therapy (n = 71) or structured clinical management (n = 63) and treated for 18 months. The investigators found that patients assigned to mentalization-based psychodynamic therapy, compared to structured clinical management, showed a steeper decline of both self-reported and clinically significant problems, including suicide attempts and hospitalization.

A manualized form of dynamic therapy, transference-focused therapy (Kernberg, Selzer, Koenigsberg, Carr, & Appelbaum, 1989), has also been investigated as a treatment for BPD in several studies. An uncontrolled study of 23 female patients with BPD treated with a year of transference-focused psychotherapy demonstrated improvements in the severity of self-injurious behavior, fewer hospitalizations, and fewer suicide attempts in the year following treatment compared with the year prior to therapy (Clarkin et al., 2001). In another uncontrolled study of 19 patients with BPD evaluated after 48 sessions of transference-focused psychotherapy, positive changes in impulsivity and affective instability were observed (Lopez, Cuevas, Gómez, & Mendoza, 2004). As mentioned, results of a large, randomized (type 1) clinical trial indicate that, in the treatment of BPD, transference-focused therapy yielded improvements in symptoms and functioning equivalent to DBT and supportive psychotherapy (Clarkin et al., 2007). However, on psychodynamic measures of attachment patterns and reflective functioning, transference-focused therapy was superior to DBT and supportive therapy (Levy et al., 2006). In another RCT, Doering and colleagues (2010) found that transference-focused psychotherapy (n = 52) was superior to treatment by experienced community psychotherapists (n = 52) in the treatment of BPD (type 1).

The type 1 study by McMain and colleagues (2009), described in the previous section on DBT, also involved a psychodynamic therapy condition. Although this treatment condition was referred to in the article as general psychiatric management, it consisted of a psychodynamic therapy combined with symptom-targeted medication. There was no significant difference between the DBT and general psychiatric management conditions in the number of medications used per patient in the trial. As mentioned, the psychodynamic group achieved equal outcomes to DBT on all outcome measures.

In a small (n = 5) uncontrolled study, brief cognitive analytic therapy (an integration of cognitive theory and some facets of psychodynamic therapy) was found to result in improvements in the severity of BPD (Wildgoose, Clarke, & Waller, 2001). A larger RCT (type 1), however, found no difference at 24 months between 24 sessions of cognitive analytic therapy (n = 41) and manualized good clinical care (n = 37) in the treatment of adolescents who fulfilled two to nine of the *DSM-IV* criteria for BPD (Chanen et al., 2008). A final small, pilot/feasibility study (type 3) found that a manual-based psychodynamic therapy (n = 15) appeared promising (relative to treatment as usual, n = 15) as a treatment for patients with BPD and co-occurring alcohol use disorder (Gregory et al., 2008).

Cognitive therapy has also been adapted to the treatment of BPD (Layden, Newman, Freeman, & Byers Morse, 1993). Results from an open trial (single treatment group; type 3 study) investigating cognitive therapy for BPD (n = 32) (Brown, Newman, Charlesworth, Crits-Christoph, & Beck, 2004) indicated that clinically important decreases in

suicidal ideation, depressive symptoms, and number of borderline symptoms were evident at termination (1 year) and at the 18-month follow-up assessment. More compelling evidence has been reported in a randomized study (type 2) conducted in France that compared cognitive therapy (n = 33) to Rogerian supportive therapy (n = 32). One year of cognitive therapy was found to retain patients in therapy longer, to have earlier positive effects on hopelessness and impulsivity, and to demonstrate better long-term outcomes on global measures of improvement (Cottraux et al., 2009). However, another RCT (type 1) reported mixed results, with no difference over 2 years between cognitive therapy (n = 54) and treatment as usual (n = 52) in terms of a composite outcome that combined suicidal acts, inpatient hospitalizations, and accident/emergency contact (Davidson et al., 2006). A significant advantage for cognitive therapy was evident in regard to reductions in suicidal acts.

Young (1994) has developed a version of cognitive therapy ("schema therapy") that integrates a focus on maladaptive beliefs or schemas with experiential techniques. A case series of six patients showed that the approach has some promise in the treatment of BPD (Nordahl & Nysæter, 2005). In addition, a randomized (type 1) study of patients with BPD found that schema therapy (n = 44) was superior to transference-focused psychotherapy (n = 42) on measures of quality of life and retention in treatment (Giesen-Bloo et al., 2006), although questions about the adequacy of the implementation of the transference-focused therapy in this trial have been raised (the investigators had an allegiance with schema therapy), which may have led to a high attrition rate (Yeomans, 2007). An additional small study (type 2) found that schema-focused therapy (n = 16) was superior to treatment as usual (n = 16), with 94% of those who received schema-focused therapy, compared to 16% of those in treatment as usual, no longer meeting criteria for BPD at the end of treatment (Farrell, Shaw, & Webber, 2009).

A cognitive-behavioral–based treatment program (Systems Training for Emotional Predictability and Problem Solving [STEPPS]) that combines cognitive-behavioral techniques and skills training with a systems component has been described (Blum, Pfohl, St. John, Monahan, & Black, 2002). The systems component includes the involvement of other patients with BPD (in 20 weekly 2-hour group meetings), as well as other people in the patient's support system (e.g., family members, significant others, health care professionals). An uncontrolled study (type 3) found that this treatment program was effective at reducing negative behaviors and affect and BPD symptoms (Blum et al., 2002). A subsequent RCT (type 1) found that STEPPS plus treatment as usual (n = 93) was superior to treatment as usual alone (n = 72) in regard to reductions in borderline symptoms, impulsivity, negative affectivity, mood, and global functioning, but there were no differences between the groups on suicide attempts, self-harm acts, or hospitalizations (Blum et al., 2008). A modified version of STEPPS was tested for adolescents with BPD traits in an RCT (Schuppert et al., 2012) (type 2). This modified version (emotion regulation training) used the structure of STEPPS, combined with elements of DBT skills training and CBT, in a 17-week group format. No outcome differences between emotion regulation training plus treatment as usual (n = 54) in comparison to treatment as usual (n = 55) were found in this trial.

ANTISOCIAL PERSONALITY DISORDER

A recent Cochrane review (Gibbon et al., 2010) has summarized the available evidence for the efficacy of different psychosocial treatments for antisocial personality disorder based on five RCTs. The review concluded that there is insufficient trial evidence to justify using any psychological intervention for adults with antisocial personality disorder. For three of the studies in the meta-analysis, the participants with antisocial personality disorder were a subgroup of the total sample; for two studies, all participants met criteria for antisocial personality disorder. These two studies are described below.

Davidson and colleagues (2009) reported on the results of a study comparing CBT plus treatment as usual to treatment as usual alone for violent men with antisocial personality disorder. The results indicated that CBT did not improve outcomes more than treatment as usual. However, this was a small (n = 52) exploratory study (type 2).

The second study (type 1) recruited a sample of individuals with antisocial personality disorder and opioid dependence and compared a contingency management intervention to treatment as usual (methadone treatment) (Neufeld et al., 2008). The contingency management group (n = 51) had

significantly better attendance and reduced family/social problems compared to the treatment-as-usual group (n = 49), but no differences were found on other outcome measures.

OTHER PERSONALITY DISORDERS

No controlled treatment outcome studies have yet been performed for histrionic, dependent, schizotypal, schizoid, narcissistic, passive-aggressive, or paranoid personality disorder. A case study with quantitative outcome data has been published showing positive effects of cognitive therapy for a paranoid personality disorder patient (Williams, 1988). Another quantitative case study reported that functional analytic therapy produced positive outcomes in a patient with histrionic and narcissistic personality disorder diagnoses (Callaghan, Summers, & Weidman, 2003).

MIXED PERSONALITY DISORDER SAMPLES

There have been several controlled studies using a sample of mixed personality disorders. Winston and colleagues (1991, 1994) randomized 81 patients with personality disorders to two forms of brief dynamic therapy, one more cognitively oriented (brief adaptive therapy) and one more oriented toward confronting defenses and eliciting affect (modeled after Davanloo, 1980), and to a waitlist control condition. The sample consisted mostly of cluster B and C personality disorder types, as well as patients diagnosed with a personality disorder not otherwise specified (mostly with cluster C features). However, paranoid, schizoid, schizotypal, narcissistic, and borderline personality disorders were excluded. Treatment lasted on average 40 weeks, although the waitlist was on average only 15 weeks. Because of this confound of treatment condition with time, this study is classified as a type 2 study. The results showed that both forms of brief dynamic therapy produced substantial improvements across multiple outcome measures, including general psychiatric symptoms, social adjustment, and target complaints. At follow-up assessments, obtained at 1.5 years on average after the end of therapy, the gains in improvement were maintained on target complaints (the only outcome measured).

In another study by the same group, Hellerstein and colleagues (1998) described the results of a study involving mixed personality disorder patients who received 40 sessions of supportive therapy (n = 24) or short-term dynamic psychotherapy (n = 25). Thirty-five percent of the patients dropped out from treatment. There were no differences between the treatment modalities at midphase (week 20), termination, or the 6-month follow-up. However, within-group effect sizes (intake to termination) were large on all outcome measures.

An RCT (type 1) compared the efficacy of 40 sessions of supportive-expressive psychoanalytic psychotherapy (n = 80) with that of community-delivered psychodynamic therapy (n = 76) for patients diagnosed with any *DSM-IV* personality disorder (Vinnars et al., 2005). In both treatment conditions, the global level of functioning improved, and there were decreases in the prevalence of patients fulfilling criteria for a personality disorder diagnosis, personality disorder severity, and psychiatric symptoms. There were no outcome differences between the two treatments. During the 1-year follow-up, patients who received supportive-expressive psychotherapy made significantly fewer visits to the community mental health centers than the patients who received community-delivered psychodynamic therapy.

Hardy and colleagues (1995) reported on the 27 cluster C personality disorder patients out of the 114 depressed patients included in the Sheffield 2 study (Shapiro et al., 1994). Clusters A and B were not assessed in that study. In this type 2 study, white-collar, employed patients received either 8 or 16 sessions of either cognitive or psychodynamic psychotherapy. At the end of treatment, cluster C personality disorder patients continued to display significantly more severe symptoms than non–cluster C personality disorder patients if they had received dynamic therapy, but not if they had received cognitive therapy. Karterud and colleagues (1992) presented the results of the effectiveness of day hospital community treatment for decompensated personality disorder patients. In this type 3 study, 97 patients were prospectively followed; 74 had a personality disorder diagnosis (34 BPD, 13 schizotypal personality disorder, and 27 other personality disorder [two thirds of which were cluster C]). All but the schizotypal personality disorder patients improved significantly on the SCL-90 and Health Sickness Rating Scale at discharge (mean stay was 171 days [standard deviation of 109]).

Monsen, Odland, Faugli, Daae, and Eilertsen (1995) reported on the results of treating 25 patients

(23 of whom had a diagnosis of a personality disorder) with psychodynamic therapy based on object relations theory and self-psychology. Treatment lasted on average a little bit more than 2 years. Patients were assessed at termination and again 5 years after termination. At the end of treatment, substantial change was found on measures of symptoms, affect consciousness, and defenses. In addition, 75% of the patients who had an Axis I disorder at intake no longer qualified for an Axis I disorder at termination. Seventy-two percent of the patients with Axis II disorders no longer qualified for the disorder at termination. The gains were maintained at the 5-year follow-up.

Høglend (1993) compared 15 patients with personality disorders in comparison to 30 patients without personality disorders (type 2 study). The treatment was psychodynamic therapy of brief to moderate length (9 to 53 sessions) that was based on the approaches of Sifneos (1979) and Malan (1976). At termination, the personality disorder patients evidenced less change than the patients without personality disorder, but at the 4-year follow-up there was no difference. For the personality disorder patients, the number of treatment sessions was significantly related to the acquisition of insight and dynamic change at follow-up. Thus, length of treatment appeared to be a crucial factor in producing positive outcomes for the personality disorder patients (but not the patients without personality disorder).

In a nonrandomized (type 2) comparison using a mixed personality disorder sample, Chiesa and Fonagy (2000) compared the effectiveness of a residential treatment based on a combination of a sociotherapeutic intervention (e.g., daily unit meetings, community meetings, structured activities, co-responsibility planning of the running of the therapeutic community, dance therapy) and formal psychoanalytical psychotherapy (individual and in small groups) to a step-down program that consisted of a short-term residential stay followed by outpatient group psychoanalytic psychotherapy. At 1 year, and continuing through a 3-year follow-up, the stepped-care model was significantly more effective than the pure inpatient model (Chiesa & Fonagy, 2000). In another nonrandomized (type 2) study of mixed personality disorders, the step-down program was compared again with a long-term residential program and with general community psychiatric care (medications, supportive outpatient therapy, hospitalization as needed; Chiesa, Fonagy, Holmes, & Drahorad, 2004). The results again favored the stepped-down approach. Similarly, a program model of outpatient group psychodynamic therapy following a brief period of more intensive treatment (day treatment) was also supported by an uncontrolled (type 3) study in Norway (Wilberg et al., 2003). The treatment program in these studies, however, was not standardized, so the exact nature of the programs is unclear. Abbass, Sheldon, Gyra, and Kalpin (2008) conducted an RCT (type 2) comparing short-term dynamic therapy (Davanloo [1980] approach) ($n = 14$) to a minimal-contact, delayed treatment control group ($n = 13$) for *DSM-IV* personality disorders. Results indicated that patients treated with short-term dynamic therapy improved significantly more than controls on all primary outcome measures.

The most recent study (type 1) of mixed personality disorders compared 24 sessions of cognitive analytic therapy ($n = 38$) to treatment as usual ($n = 40$) (Clarke, Thomas, & James, 2013). The sample consisted of a range of cluster A, B, and C personality disorder diagnoses: 88% of the sample had two or more personality disorders, and 53% displayed diagnoses across two clusters and 28% across all three clusters. BPD was diagnosed in 68% of participants. However, patients who engaged in self-harming at least monthly were excluded from the trial. The results indicated that cognitive analytic therapy was more effective than treatment as usual: Participants receiving cognitive analytic therapy showed reduced symptoms and experienced substantial benefits compared with the treatment-as-usual controls, who showed signs of deterioration over the treatment period.

PERSONALITY DISORDERS AS MODERATORS OF TREATMENT OF OTHER PSYCHIATRIC DISORDERS

Reich (2003), Reich and Vasile (1993), and Reich and Green (1991) have reviewed studies of the relation of personality traits and personality disorders to the outcome of treatments (both psychosocial and psychopharmacological) for other psychiatric conditions. Examination of the studies in these reviews, plus some more recent studies that investigate specific personality disorders and specific psychosocial treatments, reveals the following findings:

- Antisocial personality disorder (without a co-occurring diagnosis of depression) predicted

poor outcome from cognitive therapy and psychodynamic therapy for opiate addiction (Woody, McLellan, Luborsky, & O'Brien, 1985).

- Avoidant personality disorder was associated with relatively poorer outcome for agoraphobia from exposure therapy (Chambless, Renneberg, Goldstein, & Gracely, 1992) or from exposure therapy and additional anxiety management and group and individual therapy (Chambless, Renneberg, Gracely, Goldstein, & Fydich, 2000).
- Schizotypal personality disorder was associated with poor outcome of behavior therapy for obsessive-compulsive disorder (Minichiello, Baer, & Jenike, 1987).
- Presence of a personality disorder predicted poor outcome of cognitive-behavioral group therapy for social anxiety (Turner, 1987) and panic disorders (Mennin & Heimberg, 2000).
- Patients with personality disorders show slower response to imipramine plus interpersonal psychotherapy for recurrent unipolar depression (Frank, Kupfer, Jacob, & Jarrett, 1987).
- Patients with a diagnosis in the anxious cluster of personality disorders evidenced much poorer outcome with imipramine plus interpersonal therapy for recurrent unipolar depression (Pilkonis & Frank, 1988).
- A comorbid personality disorder was associated with higher rates of recurrence of depressive episodes and shorter time to recurrence over 2 years of maintenance interpersonal psychotherapy for patients with recurrent depression who were initially treated to remission (Cyranowski et al., 2004).
- Patients with BPD have relatively poorer outcomes, and incur higher treatment costs, following brief cognitive therapy for recurrent self-harm, than those without this diagnosis (Tyrer et al., 2004).
- Combined medication plus psychotherapy (brief psychodynamic therapy) is more effective than medication alone for depressed patients with comorbid personality disorders, but not more effective for those without personality disorders (Kool, Dekker, Duijsens, de Jonghe, & Puite, 2003).
- The number of personality disorders rather than presence or absence of any personality disorder was predictive of the outcomes of brief interpretive and brief supportive psychotherapies (Ogrodniczuk et al., 2001).

In group therapy, the presence of a patient with BPD may be detrimental to treatment outcome for other patients. Cloitre and Koenen (2001) found that, in interpersonally oriented group therapy for women with posttraumatic stress disorder, groups that had at least one member with BPD showed less change than did groups that did not have any members with BPD.

Presence of a personality disorder, however, does not always lead to poor outcomes. Presence of a personality disorder did not predict outcome of behavioral treatment of panic disorder in one study (Ramnero & Ost, 2004), but it did predict relapse following behavioral treatment in another (Fava et al., 2001). Presence of a personality disorder also did not have an impact on outcome (prevalence of posttraumatic stress disorder) among women with chronic posttraumatic stress disorder who received prolonged exposure therapy (Hembree, Cahill, & Foa, 2004). In long-term group psychoanalytic therapy, presence of a personality disorder was not related to outcome (Lorentzen & Høglend, 2004). Kuyken, Kurzer, DeRubeis, Beck, and Brown (2001) reported that it was not personality disorder status per se but rather the presence of maladaptive and paranoid beliefs that predicted the outcome of cognitive therapy for depression.

In some studies, patients with selected personality disorders fared better in certain types of treatments. For example, Longabaugh and colleagues (1994) investigated the extent to which antisocial personality disorder moderated the treatment of alcohol abuse. Thirty-one alcohol-abusing patients with antisocial personality disorder were compared with 118 alcohol abusers without antisocial personality disorder randomly assigned either to a group extended cognitive-behavioral treatment (which included stimulus control, rearranging consequences, restructuring cognitions, assertion training, problem solving for alternatives to drinking, and dealing with slips/relapses) or to relationship-enhanced CBT (involving functional analysis, enhancing reinforcements in relationships with partners, using partners' relationship to reinforce abstinence, and educational/didactic sessions for partners). A significant interaction was found for antisocial personality disorder by treatment modality for the average number of drinks consumed on a drinking day, with patients with antisocial personality

disorder in the extended cognitive-behavioral treatment having the fewest drinks (about two on a drinking day) and patients with antisocial personality disorder in the relationship enhancement condition having the most (about eight). The patients without antisocial personality disorder had an intermediate level of drinking on a drinking day in both treatment conditions. This interaction, however, was not found for percent of days abstinent. At the 13- to 18-month follow-up, a main effect for antisocial personality disorder emerged, with antisocial personality disorder patients showing more days abstinent than those without antisocial personality disorder.

Rosenblum and colleagues (2005) also found an interaction of antisocial personality disorder and treatment type. In this study, substance-abusing patients with antisocial personality disorder had relatively better outcomes in group cognitive-behavioral therapy than in group motivational therapy. Similarly, Messina, Farabee, and Rawson (2003) found that cocaine-dependent patients with antisocial personality disorder were more likely to be abstinent following treatment, particularly contingency management, than those without antisocial personality disorder.

A moderating (interaction) effect of cluster C personality disorders was found by Milrod and colleagues (2007). In this study, patients with panic disorder and co-occurring cluster C personality disorder improved more in psychodynamic therapy compared to applied relaxation, while this between-group effect was less for those without a cluster C personality disorder diagnosis.

Barber and Muenz (1996) reported that features of two personality disorders, avoidant and obsessive-compulsive, interacted with type of psychotherapy in the treatment of depression. Using data from the Treatment of Depression Collaborative Study (Elkin et al., 1989), Barber and Muenz (1996) found that interpersonal psychotherapy produced better outcomes for depressed patients with features of obsessive-compulsive personality disorder, but cognitive therapy produced better outcomes for depressed patients with features of avoidant personality disorder (type 2 study).

In the treatment of public speaking anxiety among patients with social phobia, the presence of avoidant personality disorder did not predict outcome (i.e., treatment was equally successful in those with and without avoidant personality disorder) in one study (Hofmann, Newman, Becker, Taylor, & Roth, 1995). There may be ways in which standard treatment can be enhanced or improved to more effectively treat those with a (non-personality disorder) psychiatric disorder who have a comorbid personality disorder. For example, a case study by Walker, Freeman, and Christensen (1994) used restricted environmental stimulation to successfully enhance the exposure treatment of obsessive-compulsive disorder in a patient with schizotypal personality disorder. Although this treatment focused on the obsessive-compulsive disorder and not the schizotypal personality disorder per se, restricted environmental stimulation therapy was incorporated because of the attentional problems found with patients with schizotypal personality. Thus, this treatment may have other applications for schizotypal personality disorder as a means of increasing attentional focus.

SUMMARY OF RECOMMENDATIONS BASED ON TREATMENT OUTCOME LITERATURE

It is obvious that the systematic study of treatment efficacy with personality disorders remains in its infancy. With few type 1 studies published yet for all personality disorders with the exception of BPD, it is difficult to make recommendations with a high degree of confidence. Linehan's DBT is the most well-established treatment, with several RCTs documenting its efficacy. However, recent studies appear to question whether DBT is uniquely efficacious, in that other credible psychotherapies have yielded similar results. There is also evidence that psychodynamically oriented treatment is effective for BPD. Other promising treatments for BPD include adaptations of cognitive therapy and schema-focused therapy. Behavior therapy is promising in the treatment of avoidant personality disorder, but the specific form of behavior therapy may need to be tailored to patients' types of interpersonal problems, with graded exposure better when distrust is an issue and intimacy-focused social skills training preferable when resisting others' demands is the major interpersonal problem in patients with avoidant personality disorder. Psychodynamic therapy, particularly longer term and involving stepped-down care beginning with residential care and then moving to outpatient treatment, appears useful for the treatment of mixed personality disorders, as does cognitive analytic therapy. One clear recommendation can be made based on a consistent finding across many

studies: Standard brief treatments for psychiatric disorders other than personality disorders often fail when personality disorder pathology is also present, and therefore the clinician should be alert to the presence of a comorbid personality disorder and reevaluate the selection of treatment modality if progress is not made within the period of brief therapy. Consistent with this recommendation are the results of Kopta, Howard, Lowry, and Beutler (1994), who found that characterological symptoms that are typical of personality disorders improve slowly, with only 59% of outpatients achieving clinically significant change on such symptoms after 52 treatment sessions.

FUTURE DIRECTIONS IN THE TREATMENT OF PERSONALITY DISORDERS

The studies reviewed above begin to point to some promising developments in the treatment of personality disorders. First, we can predict that there will likely need to be modification of the existing treatments of common psychiatric disorders to take into account personality disorder pathology. These modifications should include the lengthening of brief treatments and greater attention to the longstanding rigid belief systems and maladaptive interpersonal patterns of personality disorder patients, rather than a focus only on symptoms or recent triggers. A second major direction will be the matching of patients to treatment modalities. This matching may occur at the level of the personality disorder syndrome, in view of Barber and Muenz's (1996) finding that depressed patients with features of avoidant personality disorder do better in cognitive therapy but depressed patients with features of obsessive-compulsive personality disorders fare better in interpersonal therapy. These authors have shown that using these two diagnostic categories (either dimensionally or categorically) could be helpful in matching patients to either cognitive or interpersonal psychotherapy. Alternatively, matching patients to treatment according to patient attributes that either underlie the distinctions between personality disorders or are other salient patient variables not captured in the current system may also take place. For example, Beutler, Mohr, Grawe, and Engle (1991) suggest that impulsivity/external coping style and resistance/reactance are two important dimensions for which there is preliminary evidence for the matching of patients to treatments. Thus, rather than using the diagnosis of antisocial personality disorder as a basis for recommending a more structured treatment modality, the underlying dimensions of impulsivity and low socialization that characterize but do not uniquely define antisocial personality disorder might be more salient for treatment selection. The hybrid dimensional system included in Section III of *DSM*-5 might be a useful starting point for such matching studies.

Another direction for the future is the movement toward psychotherapy integration. In fact, Linehan's DBT already integrates techniques from a wide variety of approaches. With personality disorders, such integration might be especially important because of the diverse set of problems that characterize these patients. Thus, a successful treatment might need elements of exposure therapy, understanding and modification of longstanding cognitive/interpersonal patterns, practice in new behaviors, and attention to disruptions in the therapeutic relationship (transference). Psychosocial and psychopharmacological interventions will also be examined in combination for personality disorders as a way of managing the symptoms while also treating the underlying psychological processes. Significant advances in the treatment of personality disorders can be expected to have important public health impacts, given the prevalence of these disorders and the impairment in social and occupational functioning associated with them.

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28

Psychopharmacological Treatment of Personality Disorders

M. Mercedes Perez-Rodriguez
Larry J. Siever

Despite the lack of approval by the U.S. Food & Drug Administration (FDA), drugs are used widely to treat personality disorders, particularly borderline personality disorder (BPD), based on their effects known from clinical trials in other psychiatric disorders (off-label use). The role of medications in personality disorders is limited to moderate effects on some but not all of the symptom domains, and there are no medications available that improve global severity of any personality disorder as a whole. In BPD, evidence is strongest for second-generation antipsychotics (SGAs) and mood stabilizers, while dietary supplements such as omega-3 fatty acids hold some promise. However, medications have limited effectiveness and are still viewed as adjunctive to other forms of treatment, particularly psychotherapy.

INTRODUCTION

Medications are increasingly used to treat personality disorders as a result of the increasing number and quality of clinical trials available and the growing knowledge base about the biological correlates of the personality disorders. However, compared to other psychiatric disorders, research into the psychopharmacology of personality disorders is still in its infancy. There are a limited number of clinical trials, often with small sample sizes, and the evidence for symptom improvement is modest at best.

Personality disorders are commonly divided into three clusters: cluster A ("odd") disorders, cluster B ("dramatic") disorders, and cluster C ("anxious") disorders. The most extensive studies of the pharmacotherapy of personality disorders have examined the cluster B disorders, particularly BPD, and schizotypal personality disorder (SPD) in cluster A. Several case reports of the treatment of cluster C avoidant personality disorder have also been reported. However, the evidence for other personality disorders is very limited.

The pharmacotherapy of personality disorders represents a relatively new frontier of psychopharmacology. Traditionally, personality-disordered patients have been treated with psychotherapy and have been thought unresponsive to pharmacological intervention. However, advances in the field over the past three decades have challenged that perspective. A biological approach to the personality disorders has questioned the traditional separation of Axis I and Axis II diagnoses, resulting in the elimination of the axis system in the latest version of the *DSM*, *DSM-5* (American Psychiatric Association, 2013).

Research into the neurobiological basis of psychiatric disorders increasingly focuses on dimensions within domains of psychopathology that cut across diagnoses, and on their underlying neural circuits and molecular and genetic modulators. The Research Domain Criteria initiative (RDoC; Insel et al., 2010) is an example of this approach, which converges with recent efforts to examine the neurobiology of personality disorder traits. Thus, there is an

emerging neurobiology of personality disorders based in the brain circuit abnormalities underlying dimensions such as affective dysregulation, disinhibited aggression, anxiety/avoidance, cognitive/perceptual dysregulation, and social detachment/isolation. The following is a summary of the neurobiology and psychopharmacology of the personality disorders, including specific challenges.

The main challenges in the systematic investigation of biological etiologies and treatments for personality disorders are (1) the existence of significant clinical heterogeneity even within one personality disorder diagnostic category; (2) the overlap in symptomatology and comorbidity among the various personality disorder diagnoses; (3) the high symptom overlap and comorbidity with Axis I and II disorders; and (4) the limited reliability in the diagnostic assessment of the personality disorders.

Clinical Heterogeneity and Overlap of Axis II Disorders

The polythetic definition of personality disorders—each diagnosis requires meeting a certain number of criteria out of a larger set of criteria (e.g., five out of nine criteria for BPD)—means that it is possible for two people to meet the criteria for a given personality disorder and yet have very different personality traits. This heterogeneity is a major problem in assessing the effect of a medication. For example, it is possible to have a clinically heterogeneous group of patients in a study even though all the patients meet criteria for the same personality disorder. Moreover, different personality disorders share some of the criteria under the *DSM-IV* and *DSM-5* categorization, and often patients meet criteria for more than one type of personality disorder (Grant et al., 2008; Lenzenweger, Lane, Loranger, & Kessler, 2007; Skodol et al., 2005).

Reliability of Assessment Tools

Methodological problems in designing studies of patients with personality disorders include limited reliability assessment and limited longitudinal stability of the diagnoses. For example, BPD seems to be less stable across time points than expected for personality disorders, with high rates of remission in follow-up studies (Skodol et al., 2005; Zanarini, Frankenburg, Hennen, Reich, & Silk, 2006); in fact, there is an inverse relationship between age and prevalence of BPD in the general population (Grant et al., 2008).

Assessment instruments are of limited efficacy due to modest test–retest and intratest reliability (Gitlin, 1993). These difficulties in assessment may be related to our limited understanding of how to differentiate a personality disorder trait from the adaptive personality traits.

Developing standardized measures of change in personality disorder symptoms poses a challenge given that many of these symptoms are "persistently transient" (e.g., mood lability in BPD). Long follow-up periods are preferred to delineate the natural course of episodic personality traits such as mood lability. However, symptoms such as unstable interpersonal relationships or suspiciousness may interfere with the maintenance of the treatment alliance until completion of the research study, leading to high dropout rates.

Because most of the personality disorder symptoms are context dependent and reactive to the environment, it is critical to keep all nonpharmacological variables (such as milieu of the research setting and interactions with the research team) consistent across subjects and time points for each study.

The Need for Multiple Approaches to Defining and Treating Personality Disorders

Skepticism about the categorical nature of personality disorders (Eaton et al., 2011; Widiger, Livesley, & Clark, 2009) has been fueled by the high comorbidity and symptom overlap among personality disorders and between personality disorders and other psychiatric diagnoses (i.e., *DSM-IV* Axis I diagnoses). As a result, alternate dimensional models have been proposed. Some of these dimensional models are based on the Five Factor Model (Costa & Widiger, 2002). Another model classifies dimensions based on their prominence in particular personality disorders and their presumed underlying neurobiology, conceptualizing the core dimensions of personality as cognitive/perceptual distortions (cluster A, "odd"), affective lability and impulsivity/aggression (cluster B, "dramatic"), and anxiety (cluster C, "anxious").

Evidence for these dimensional approaches is derived from studies of biological correlates of personality traits and family and twin studies supporting the heritability of dimensions (Torgersen et al., 2000;

Trestman, deVegvar, & Siever, 1995). Large-scale twin studies also support a dimensional model for personality disorders, including four factors: internalizing, externalizing, anhedonic/introversion, and cognitive/relational disturbance (Kendler et al., 2011; Roysamb et al., 2011); this model also questioned the division between Axis I and II in *DSM-IV*. For example, antisocial personality disorder was most closely related to Axis I substance abuse disorders, and dysthymia was most closely linked to avoidant and dependent personality disorders.

The controversy about which approach (categorical vs. dimensional) is more valid led to the proposal of a hybrid system including both approaches for *DSM-5* (Rationale for the Proposed Changes to the Personality Disorders Classification in DSM-5: http://www.dsm5.org/ProposedRevision/Pages/proposedrevision.aspx?rid=17#). The final approved version of *DSM-5* maintains the categorical model and criteria for the 10 *DSM-IV* personality disorders and includes the newly proposed trait-specific classification system in a separate area of Section III.

One challenge in targeting a particular personality dimension is that the neural substrate for a specific dimension may include abnormalities in more than one neurotransmitter system (Gurvits, Koenigsberg, & Siever, 2000). Moreover, treating one core dimension does not address the complex clinical syndrome of the personality disorder as a whole. Finally, in defining a core dimension in personality disorders, a distinction must be made between traits and state symptoms. Despite these limitations, the dimensional approach avoids the problems of clinical heterogeneity and high comorbidity and provides a framework for inquiry into the interrelationships among types of behavior, their modulation by neurotransmitters, and pharmacological interventions.

In summary, categorical and dimensional approaches can be used for investigating psychopharmacological treatments for personality disorders. A categorical approach allows a more clinical conceptualization of the personality disorders but may not allow us to measure change in response to medication in a meaningful way, given the high symptom overlap and comorbidity with other disorders, and an incomplete distinction between state symptoms versus traits. A dimensional approach allows for more precise measuring of individual traits but may not fully capture the complex entity of each personality disorder. Although each approach has recognized limitations, each can also offer valuable frameworks within which these disorders can be further investigated.

We now turn to a review of the pharmacological treatments of personality disorders and the psychobiological findings that prompted the use of such treatments.

CLUSTER A DISORDERS ("ODD" CLUSTER)

Schizotypal personality disorder (SPD) has been the most carefully studied of the cluster A disorders. SPD, part of the schizophrenia spectrum, is characterized by attenuated symptoms similar to those present in chronic schizophrenia. The SPD population offers a unique opportunity to investigate the neurobiology and pathophysiology of schizophrenia without the confounds of medication and more severe functional impairment (Siever et al., 2002a). SPD is more common among the relatives of schizophrenic patients in comparison to control patients (Silverman et al., 1993), and having at least one parent with SPD increased the risk to develop both SPD and schizophrenia among siblings of probands with schizophrenia (Baron, Gruen, & Asnis, 1985).

Many of the abnormalities in brain structure and function (Kirrane & Siever, 2000; Koenigsberg et al., 2005; Siever et al., 2002a) and psychophysiological measures (e.g., smooth pursuit eye movements, backward masking tests, and continuous performance tasks) described in schizophrenia are also found in SPD (Siever, 1991). These findings support the concept of a spectrum of schizophrenia-like disorders. Psychobiological investigations into SPD, based on a dimensional model of symptoms, have also supported the relationship between SPD and schizophrenia and provide a logical starting point for psychopharmacological interventions for this personality disorder.

The neurobiology of SPD may be conceptualized in relation to its core traits, which broadly stem from disturbances within the cognitive/perceptual domain. These cognitive/perceptual disturbances result in impairments in attention to the environment, discrimination among stimuli, and information processing. Clinically, these impairments may translate into psychotic-like symptoms (such as magical thinking, ideas of reference, or perceptual distortion), deficit-like symptoms (such as poor interpersonal relatedness or social detachment), and cognitive disorganization (such as deficient performance on

cognitive, psychophysiological, and attentional testing) (Siever & Weinstein, 2009).

Psychotic-Like Symptoms in Schizotypal Personality Disorder

Psychotic-like symptoms are characteristic of SPD. Higher symptom severity along a dimension of psychotic-like perceptual distortions has been correlated with higher measures of dopaminergic activity. For example, cerebrospinal fluid homovanillic acid (HVA; the major dopamine metabolite) concentrations in SPD patients correlate significantly with psychotic-like symptoms and were significantly higher than in patients with other personality disorders and healthy controls (Siever et al., 1991). These findings support the use of dopamine antagonists in the treatment of SPD. Given the known efficacy of antipsychotic medications in schizophrenia, their effect on psychotic-like symptoms in SPD has also been investigated (Table 28.1). However, the majority of these studies primarily targeted subjects with BPD and described secondary findings for patients who also met criteria for SPD. The single study of first-generation antipsychotics including only SPD patients (Hymowitz et al., 1986), using a single-blind design, did not find any improvement in psychotic-like symptoms after treatment with haloperidol. The three double-blind, placebo-controlled studies of mixed populations of SPD and BPD patients (Cowdry & Gardner, 1988; Goldberg et al., 1986; Soloff et al., 1989) show an association between low-dose antipsychotic use and broad improvements in symptom scales of psychoticism, anxiety, depression, hostility, and rejection sensitivity. However, one of those studies (Cowdry & Gardner, 1988) included patients with severe affective instability, questioning the generalizability of these findings to the more typically emotionally constricted SPD subjects. Other non–placebo-controlled studies (Jensen & Andersen, 1989; Serban & Siegel, 1984) found moderate, global improvements in mixed BPD and SPD populations after treatment with antipsychotic medication.

The second-generation antipsychotic (atypical) medications (SGAs) are promising candidates for the treatment of SPD because of their potential for targeting negative symptoms (Javitt, 1999; Lane, Liu, & Chang, 1999). One open-label study of the SGA olanzapine in the treatment of dysthymic borderline patients—most of whom also met criteria for SPD (Schulz et al., 1999)—found robust improvement over the 8-week treatment period in global scores from five rating scales (see Table 28.1). Our group (Koenigsberg et al., 2003) completed a 9-week placebo-controlled, double-blind study of low-dose risperidone in the treatment of nondepressed SPD patients, only 20% of whom had comorbid BPD. We found statistically significant decreases in Positive and Negative Syndrome Scale (PANSS) negative and general symptom scores by week 3 and PANSS positive score by week 7 in the risperidone group compared with the placebo-treated group. Thus, it appears that schizotypal symptomatology in mixed SPD/BPD populations is modestly and broadly responsive to low-dose antipsychotic medication.

Given the state of dopamine antagonism induced by antipsychotic medications and the correlations between increased plasma and cerebrospinal fluid dopaminergic metabolites and psychotic-like symptoms in SPD, it is tempting to hypothesize that psychotic-like symptoms in SPD would be particularly responsive to antipsychotic medications. Future double-blind, placebo-controlled trials with primarily SPD subjects are needed to refine the role for these medications in SPD.

The attenuated nature of psychotic symptoms in SPD patients—compared to those found in schizophrenia—is believed to be due to better buffering of subcortical dopaminergic activity (Siever & Davis, 2004; Siever & Weinstein, 2009). This hypothesis is supported by the results of functional and structural imaging and neuroendocrine challenge studies. This better buffering may result in lower responsiveness to stress by subcortical dopaminergic systems, which may protect against overt psychosis (Mitropoulou et al., 2004; Siever & Davis, 2004; Siever & Weinstein, 2009).

Despite this better buffering, dopaminergic agonism might be expected to worsen the psychotic-like symptoms of SPD. Consistent with this theory and supporting the inclusion of SPD in the psychotic spectrum disorders, a study in a small sample of SPD/BPD and BPD patients with high affect lability showed that, after amphetamine administration, SPD subjects had significantly higher Brief Psychiatric Rating Scale (BPRS) scores of thought disturbance and self-rated psychoticism compared with BPD subjects (Schulz, Cornlius, Schulz, & Soloff, 1988).

TABLE 28.1 Antipsychotic Studies: Borderline Personality Disorder and Schizotypal Personality Disorder

Study	*Diagnosis*	*Study Design*	*Comment*
Goldberg et al. (1986)	N = 50 BPD and/or SPD patients (BPD with at least one prior psychotic episode)	Type 1 study: thiothixene (average 8.6 mg), 12 weeks, double-blind, placebo-controlled	Thiothixene led to improvement of psychotic-like/obsessive/phobic anxiety symptoms; no effect on depression.
Cowdry & Gardner (1988)	N = 16, female BPD outpatients; all characterized as "seriously ill with severe dysphoria in setting of rejection, and dyscontrol behavior such as assaultiveness, cutting, overdose"; of these, 6 patients also SPD	Type 1 study: tranylcypromine, trifluoperazine, carbamazepine, alprazolam; 6 weeks; double-blind, placebo-controlled	Tranylcypromine led to improved global and mood scores, improved impulsivity, but no effect on behavioral dyscontrol; trifluoperazine showed a trend toward broad symptomatic improvement; carbamazepine showed improvement of impulsivity and behavioral dyscontrol; alprazolam led to increases in suicidality and dyscontrol.
Soloff et al. (1989)	N = 90 inpatients with BPD, mixed SPD/BPD symptoms, and a small number of SPD patients	Type 2 study: amitriptyline (100– 175 mg) or haloperidol (4–16 mg); 5 weeks; placebo-controlled	Haloperidol led to global improvements, including hostile depression and impulsive ward behavior, especially if patient had severe schizotypal symptoms, hostility, or suspiciousness. Amitriptyline not as effective as haloperidol for anxiety and hostility; not effective on core depressive symptoms.
Serban & Siegel (1984)	N = 52 outpatients with SPD (14), BPD with prior psychotic episode (16), mixed SPD/BPD (16)	Type 2 study: haloperidol or thiothixene (4–12 mg), 6 weeks to 3 months, double-blind	Thiothixene > haloperidol led to moderate to marked improvements in all patients for general symptoms, paranoid ideation, anxiety, ideas of reference, and depression regardless of diagnosis.
Hymowitz et al. (1986)	N = 17 SPD outpatients	Type 2 study: haloperidol (up to 12 mg, average 3.6 mg); 6 weeks; single-blind, 2-week placebo washout	Drug led to mild to moderate improvement in ideas of reference, social isolation, odd communication, and thought disorder; also GAS scores increased.
Jensen & Andersen (1989)	N = 5 SPD, 5 BPD inpatients	Type 3 study: amoxapine (up to 300 mg); 3 weeks minimum; open label, no placebo; oxazepam prn agitation (36–42 mg qd)	SPD subjects showed broad improvement in BPRS (schizophrenia subscale) and HDRS scores. BPD subjects showed no improvement.
Chengappa et al. (1999)	N = 7 inpatients with BPD, 6 with Axis I psychotic disorders	Type 3 study: clozapine; chart audit with mirror image design; mean dose 421 mg/day.	Decrease in number of seclusion and restraint incidents, modest improvement in GAF.

(*continued*)

TABLE 28.1 (continued)

Study	*Diagnosis*	*Study Design*	*Comment*
Schulz et al. (1999)	N = 11 community-based referrals meeting criteria for BPD and dysthymia (7 of whom also met SPD criteria)	Type 3 study: olanzapine (up to 10 mg, average 7.7 mg); open label no placebo; 8-week study.	Olanzapine led to improvement in global scores on BPRS, BDHI, BIS11, GAF, SCL-90.
Koenigsberg et al (2003)	N = 25 community and clinic referrals meeting criteria for SPD (only 20% also meet BPD criteria)	Type 1 study: risperidone (up to 2 mg) 9-week double-blind, placebo-control; 2-week placebo wash-out	Risperidone led to significantly lower PANSS negative and general score by week 3 and PANSS positive score by week 7.
Rocca et al. (2002)	N = 15 outpatients meeting criteria for BPD (4 were comorbid for antisocial personality disorder)	Type 3 study: risperidone (mean dose 3.3 mg/day); 8-week open-label no placebo trial	Significant improvement in BPRS total, hostility/suspicion, and anergia scales; HDRS; GAF; AQ
Zanarini & Frankenburg (2001)	N = 28 females meeting criteria for BPD recruited by advertisement (1 comorbid for SPD)	Type 1 study: olanzapine (mean dose 5.3 mg/day). 6-month randomized placebo-controlled double-blind	Olanzapine significantly superior to placebo in SCL-90 anger/ hostility, anxiety, paranoia, interpersonal sensitivity. Few dropouts.
Zanarini et al.(2004)	N = 45 females meeting criteria for BPD recruited by advertisement	Type 2 study: randomized double-blind non-placebo-controlled 8-week parallel comparison of olanzapine (3.3 mg), fluoxetine (15 mg), and olanzapine/fluoxetine combination (3 mg/13 mg)	Olanzapine/fluoxetine combination is more effective than fluoxetine in treating impulsivity-aggression and dysthymia. Olanzapine is more effective than olanzapine/ fluoxetine combination in treating dysthymia and equally effective in impulsivity aggression. Few dropouts.
Soler et al. (2005)	N = 60 clinically referred BPD patients	Type 2 study: 12-week randomized double-blind, placebo-controlled trial of olanzapine (8.8 mg/day). Both groups received DBT.	Olanzapine + DBT superior to DBT alone in impulsive-aggressive behaviors, emergency department visits, depression, anxiety, and CGI score.
Villeneuve & Lemelin (2005)	N = 34 BPD patients with GAF < 55	Type 3 study: 12-week open-label trial of quetiapine (mean dose = 251 mg)	Significant improvement in impulsivity, hostility, anxiety depression, GAF score, and for patients with psychotic symptom at baseline, micropsychotic symptoms.
Mobascher et al. (2006)	N = 3 female patients with BPD and psychotic symptoms	Case series open-label study of aripiprazole up to 25 mg/day + cognitive-behavioral therapy	Decreased psychotic symptoms, self-damaging and aggressive behavior in 1 case, partial response in 1 case
Pascual et al. (2006)	N = 2 patients with BPD and agitation in the emergency department	Case series naturalistic open-label study of either olanzapine 10 mg IM or ziprasidone 20 mg IM.	Significant improvement in agitation up to 6 hrs after injection vs. baseline (pretreatment)

TABLE 28.1 (continued)

Study	*Diagnosis*	*Study Design*	*Comment*
Bellino et al. (2006)	N = 14 outpatients with BPD	12-week open-label quetiapine up to 400 mg/day	Symptom improvement in HAM-A, BPRS, CGI, SOFAS, BPDSI, and BIS11
McClure et al. (2007)	N = 29 patients with SPD	Randomized, double-blind, 4 weeks of guanfacine (up to 2 mg/day) vs. placebo, followed by 4 weeks of open-label guanfacine	After 4 weeks, greater improvements from baseline in neuropsychological measures of working memory (Modified AX-Continuous Performance Task) compared to placebo
Perrella et al. (2007)	N = 29 outpatients with BPD	12-week open-label quetiapine (up to 800 mg/day)	Symptom improvement in HAM-D, BPRS Hostility and Suspiciousness, CGI, GAF, AQ
Shoja-Shafti (2006)	N = 20 female patients with BPD	8-week open-label olanzapine (10 mg/day)	Symptom reduction with olanzapine (BPRS, BDHI, GAF)
Damsaet al. (2007)	N = 25 unmedicated patients with BPD and severe agitation in the emergency department	1 or 2 doses of open-label olanzapine (10 mg IM)	Significant reductions of agitation 2 hours after the first IM olanzapine
Nickel et al. (2006)	N = 52 patients with BPD	Randomized, double-blind study of 8 weeks of aripiprazole (15 mg/day) vs. placebo	Symptom improvement on SCL-90-R, HAM-D, HAM-A, and STAXI. Improvement on SCL-90-R, HAM-D, HAM-A, and STAXI was also observed at an 18-month follow-up (Nickel et al., 2007).
Friedel et al. (2008)	N = 18 patients with BPD	Open-label study of 8 weeks of risperidone (up to 2 mg/day)	Symptom improvement on all BDRS dimensions (affective dysregulation, cognitive impairment, impulsivity and disturbed relationships) and BSI scales
Van den Eynde et al. (2008)	N = 41 patients with BPD	Open-label study of 12 weeks of quetiapine (up to 800 mg/day)	Improvement of depressive, impulsive, aggressive, and affect lability symptoms
Roepke et al. (2008)	N = 15 inpatients with BPD, histrionic or narcissistic personality disorder	Open-label quetiapine (400 mg/day) for 8 weeks	Improvement of depressive symptoms but no effect on impulsivity
Bellino et al. (2008)	N = 21 outpatients with BPD who did not respond to sertraline (100–200 mg/day) for 12 weeks	Open-label adjunctive aripiprazole (10–15 mg/day) for 12 weeks	Symptom improvement at 12 weeks compared to baseline
Adityanjee et al. (2008)	N = 16 patients with BPD	Open-label case series of 8 weeks of quetiapine (average dose in completers = 286.1 mg/day)	Significant improvement in symptoms (measured by GAF, SCL-90, BIS)
Pascual, Soler et al. (2008)	N = 60 patients with BPD	Double-blind, randomized, 12 weeks of ziprasidone (up to 200 mg) vs. placebo	No statistically significant differences between ziprasidone and placebo in the CGI-BPD or other symptoms

(*continued*)

TABLE 28.1 (continued)

Study	*Diagnosis*	*Study Design*	*Comment*
Schulz et al. (2008)	N = 314 BPD outpatients	Randomized, double-blind study of 12 weeks of olanzapine (variable dose, up to 20 mg/day) vs. placebo	Symptom improvement not significantly greater than placebo
McClure et al. (2010)	N = 25 patients with SPD	Double-blind, randomized, 12 weeks of pergolide (up to 0.3 mg/day) vs. placebo	The pergolide group showed improvements in visual-spatial working memory, executive functioning, and verbal learning and memory.
Shafti & Shahveisi (2010)	N = 28 female inpatients with BPD	Randomized, double-blind study of 8 weeks of olanzapine vs. haloperidol	Symptom improvement on the BPRS between baseline and 8 weeks, no differences between olanzapine vs. haloperidol
Zanarini et al. (2011)	N = 451 BPD outpatients	Two randomized, double-blind studies of 12 weeks of olanzapine (up to 20 mg/day) vs. placebo	Treatment with olanzapine (5–10 mg/day) was associated with significantly greater decrease from baseline to endpoint in ZAN-BPD total score relative to placebo.
Carrasco et al. (2012)	N = 49 BPD patients refractory to oral medications	Open-label study of up to 50 mg IM of long-acting risperidone every 2 weeks for up to 6 months	Decreased symptom severity, aggression scores, and anxiety and increased psychosocial functioning at 6 months
Zanarini et al. (2012)	N = 444 BPD patients who had completed 12 weeks of double-blind olanzapine or placebo	Open-label study of up to 15 mg or 20 mg of olanzapine	Continued therapy with olanzapine may sustain and build upon improvements seen with acute olanzapine treatment of patients with BPD.
Koychev et al. (2012)	N = 248 HC scoring high (SPQ score >1 SD above the mean) or average on schizotypy (within +/- 0.5 SD of the mean)	Randomized, double-blind, single dose of risperidone (400 mg), amisulpride (2 mg), nicotine (7 mg transdermal), or placebo	Amisulpride improved working memory (on N-back) in the high schizotypy group but impaired it in those with average schizotypy. Risperidone improved only those with low baseline performance.
Rosell et al. (2015)	N=16 medication-free SPD patients who met criteria for cognitive impairment (i.e., scoring below the 25th percentile on tests of working memory)	Randomized, double-blind, placebo-controlled trial of the D1 agonist dihydrexidine (DAR-0100A) (15 mg/150 mL of normal saline administered intravenously over 30 minutes on 3 consecutive days)	DAR-0100A produced significant improvements in two measures of verbal working memory, particularly in the Paced Auditory Serial Addition Test (PASAT)

AQ = Aggression Questionnaire; BPD = borderline personality disorder; BDHI = Buss-Durkee Hostility Inventory; BDRS = Borderline Disorder Rating Scale; BIS11 = Baratt Impulsivity Scale version 11; BPDSI = Borderline Personality Disorder Severity Index; BPRS = Brief Psychiatric Rating Scale; BSI = Brief Symptom Inventory; CGI= Clinical Global Impression; CGI-BPD = Clinical Global Impression Scale for BPD; DBT = dialectical behavior therapy; GAS = Global Assessment Scale; GAF = Global Assessment of Function; HAM-A = Hamilton Anxiety Scale; HDRS, HAM-D = Hamilton Depression Rating Scale; HC = Healthy controls; PANSS = Positive and Negative Syndrome Scale; SCL-90 = Hopkins Symptom Check List 90; SCL-90-R = Symptom Checklist-90-Revised; OAS-M = Overt Aggression Scale-Modified; SOFAS = Social and Occupational Functioning Assessment Scale; SPD = schizotypal personality disorder; SPQ = Schizotypal Personality questionnaire; STAXI = State-Trait Anger Expression Inventory; ZAN-PBD = Zanarini Rating Scale for Borderline Personality Disorder.

In contrast, in another study nine patients selected only based on meeting SPD criteria showed no increase in psychotic-like symptoms with amphetamine administration (Siegel et al., 1996). This is consistent with a model of two distinct symptom profiles linked to relatively increased versus decreased dopaminergic activity respectively, depending on the predominance of psychosis-like (hypervigilance and stereotypic cognitions/behaviors) or deficit-like (deficits in working memory, cognitive processing, and hedonic tone) symptoms (Siever & Davis, 2004). Those SPD patients with hyperdopaminergic states may be more responsive to treatment with dopamine antagonists and respond negatively to dopamine agonists, whereas those with normal or reduced dopaminergic function may improve with dopamine agonists (see below).

Deficit-Like Symptoms and Cognitive Disorganization in Schizotypal Personality Disorder

Neurobiological studies of the deficit-like symptoms of SPD have investigated their relationship to psychophysiological and neuroanatomical measures and indices of neurotransmitter activity. Abnormalities in smooth pursuit eye movements, backward masking tests, and continuous performance tasks correlate with deficit symptoms of SPD (Siever, 1991). Cognitive disorganization, measured by performance on psychological testing, has also been found in SPD patients. Schizotypal patients make significantly more errors on the Wisconsin Card Sort Test compared to healthy control subjects and other patients with non–cluster A personality disorders (Trestman et al., 1995). These results suggest that abnormalities in the frontal and temporal cortices may be related to the deficit symptoms of SPD.

Correlations between neurotransmitter levels and deficit-like symptoms in SPD have been investigated. Whereas higher plasma HVA levels correlate with psychotic-like symptoms in patients with personality disorders, lower plasma HVA levels may be associated with deficit-like symptoms in relatives of patients with schizophrenia and with cognitive deficits in SPD patients (Siever, Kalus, & Keefe, 1993).

Investigations of cholinergic indices in patients with schizophrenia have yielded inconsistent results (Karson, Casanova, Kleinman, & Griffin, 1993; Tandon & Greden, 1989); however, data from our laboratory suggest that the cholinergic agent physostigmine may improve performance in visuospatial delayed-response attentional tasks in SPD patients (Kirrane et al., 2001).

The above findings suggest that dopaminergic agonists may be used to treat deficit symptoms and cognitive disorganization in SPD patients. One double-blind, placebo-controlled study of amphetamine in SPD/BPD patients found that in addition to worsening of psychotic-like symptoms in the SPD group, all subjects had increased activation scores on the BPRS (Schulz et al., 1988). This might suggest an improvement in deficit symptoms such as anergia and withdrawal. Further, a preliminary study of amphetamine administration in SPD patients showed improved performance on the Wisconsin Card Sort Test (Siegel et al., 1996). In a recent randomized, double-blind, placebo-controlled trial in our center, pergolide, a dopamine agonist targeting D1 and D2 receptors, significantly improved visual-spatial working memory, executive functioning, and verbal learning and memory in SPD patients (McClure et al., 2010) (see Table 28.2).

Furthermore, our group has carried out a randomized, double-blind, placebo-controlled pilot trial (Rosell et al., 2015) of the D_1 agonist dihydrexidine (DAR-0100A) in 16 unmedicated SPD patients who met criteria for cognitive impairment. DAR-0100A produced significant improvements in a number of cognitive domains, including verbal working memory and executive function. Specifically, two measures of verbal working memory that are known to implicate cognitive impairment in SPD patients were used: the Paced Auditory Serial Addition Test (PASAT) and the N-back test (ratio of 2-back:0-back scores). Subjects who received DAR-0100A showed significantly improved performance, particularly in the PASAT, relative to those who received placebo. Despite a modest sample size, the differences in verbal working memory improvement between DAR-0100A and placebo groups were associated with large effect sizes that reached statistical significance. While this pilot study successfully demonstrated the effectiveness of a selective, full D_1 receptor agonist in enhancing working memory in patients with schizophrenia-spectrum cognitive deficits, we are currently conducting a large, randomized, placebo-controlled, crossover trial of DAR-0100A in patients with SPD using a more comprehensive neuropsychological battery of

TABLE 28.2 Pharmacology of Borderline and Schizotypal Personality Disorder: Other Agents

Study	*Diagnosis*	*Study Design*	*Comment*
Bohus et al. (1999)	N = 13 BPD patients with prominent dissociative phenomena including flashbacks	Open-label naltrexone (25–100 mg qid) for at least 2 weeks	Improvement on a self-rated questionnaire measuring dissociation, analgesia, tonic immobility, and tension, and in dissociative phenomena, tonic immobility, analgesia and flashbacks
Zanarini & Frankenburg (2003)	N = 30 female BPD patients	8-week, placebo-controlled, double-blind study of ethyl-eicosapentaenoic acid (E-EPA) and omega-3 acid)	E-EPA was superior to placebo in decreasing aggression and depressive symptoms.
Philipsen et al. (2004)	N = 14 female BPD patients	Single dose of clonidine (75 mcg or 150 mcg) on 2 separate occasions in a single-blind, randomized crossover design	Significant decrease in self-reported aversive inner tension, the urge to commit self-injurious behavior, dissociative symptoms, and suicidal ideation at 30, 60, 90, and 120 minutes after administration
Miyaoka et al. (2008)	N = 20 female outpatients with BPD	Open-label 12 weeks of *yi-gan san* (a traditional Chinese herbal medicine)	Statistically significant reduction on self-rated and clinician-rated scales (BPRS, CGI, GAF, AQ)
Golubchik et al. (2008)	N = 14 adolescent females with BPD and ADHD	Open-label 12 weeks of methylphenidate	A significant improvement was detected in both ADHD and BPD severity.
Ziegenhorn et al. (2009)	N = 18 patients with BPD and a hyperarousal syndrome, +/- PTSD	Double-blind, randomized crossover study of clonidine vs. placebo (2 weeks each)	Hyperarousal improved regardless of PTSD comorbidity.
Schmahl et al. (2012)	N = 29 unmedicated patients with BPD	Double-blind crossover design, 3 weeks of up to 200 mg/day of naltrexone and 3 weeks of placebo in randomized order	Nonsignificant decreases in intensity and duration of dissociative symptoms with naltrexone vs. placebo
Bertsch et al. (2013)	N = 40 nonmedicated, adult female patients with BPD	Randomized double-blind, single-dose intranasal oxytocin (26 IU) vs. placebo	Decrease in hypersensitivity to social threat
Amminger et al. (2013)	N = 15 adolescents with BPD and ultra-high risk criteria for psychosis	Randomized double-blind trial; 12 weeks of 1.2 g/day long-chain omega-3 polyunsaturated fatty acids (PUFAs) or placebo	Improved global functioning (GAF) and reduced symptoms of depression (MADRS), and PANSS negative symptoms, suspiciousness, tension and poor impulse control

TABLE 28.2 (continued)

Study	*Diagnosis*	*Study Design*	*Comment*
Schmechtig et al. (2013)	*N* = 233 healthy participants with medium and high schizotypy based on their scores on the Schizotypal Personality Questionnaire	Randomized double-blind, single dose of nicotine (7 mg/24 hours, transdermal), risperidone (400 mg/day), or amisulpride (2 mg/day) vs. placebo	Nicotine improved performance in antisaccade tasks in medium and high schizotypes
Wingenfeld et al. (2013)	*N* = 71 women with BPD	Placebo-controlled, crossover study; 10 mg of hydrocortisone vs. placebo	Cortisol improved hippocampal-mediated memory processes in patients with BPD alone or BPD + PTSD (but not those with BPD + MDD).

ADHD = attention-deficit/hyperactivity disorder; AQ = Aggression Questionnaire; BPD = borderline personality disorder; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression Scale; GAF = Global Assessment of Functioning; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; PANSS = Positive and Negative Syndrome Scale; PTSD = posttraumatic stress disorder.

working memory and verbal learning tasks to confirm initial findings.

Robust preclinical evidence (Franowicz & Arnsten, 2002) supports the role of noradrenergic agonists, particularly alpha-2 agonists, in enhancing working memory. Our group has carried out a trial of the alpha-2A agonist guanfacine and found that it improved neuropsychological measures of working memory in SPD patients (McClure et al., 2007).

The monoamine oxidase inhibitor (MAOI) tranylcypromine caused broad behavioral effects in one mixed SPD/BPD group (Cowdry & Gardner, 1988) (see Table 28.1), including an increased capacity for pleasure. Although this may reflect an improvement of deficit-like symptoms, it may also be due to the effect of tranylcypromine on comorbid mood disorders. Catecholaminergic agents need to be further investigated in SPD patients, with special focus on their effect on cognitive performance and on deficit-like symptoms.

Another approach to try to identify more efficient drugs for the treatment of cognitive symptoms in the schizophrenia spectrum involves the study of surrogate populations with high levels of schizotypy. Such studies showed that single, low-dose antipsychotics (amisulpride) and nicotine have positive effects on cognitive performance (e.g., working memory) and on disease biomarkers such as oculomotor deficits (Koychev et al., 2012; Schmechtig et al., 2013) (see Tables 28.1 and 28.2).

Growing evidence suggests that intranasal oxytocin, used as an adjunct in patients treated with antipsychotics, improves positive symptoms and social cognitive deficits in schizophrenia (Feifel, Macdonald, Cobb, & Minassian, 2012; Feifel et al., 2010; Goldman, Gomes, Carter, & Lee, 2011; Modabbernia et al., 2013; Pedersen et al., 2011). Whether a similar positive effect can be found in SPD remains untested.

Treatment of Comorbid Diagnoses in Schizotypal Personality Disorder

Antidepressant agents are often used in SPD based on the high rates of comorbidity between SPD and depressive disorders: 67% of individuals with SPD have at least one mood disorder, and over 70% have at least one anxiety disorder (Pulay et al., 2009). Thirty percent to 50% of SPD patients seen in clinical settings have a concurrent major depressive disorder, and 50% of patients have a history of major depressive disorder (Kaplan & Sadock, 1995). So far, however, trials with antidepressant agents in SPD have only been conducted in groups of mixed SPD/BPD patients (see Tables 28.1 and 28.3). The use of fluoxetine, up to 80 mg over a 12-week period, was investigated in a mixed group and was found to decrease obsessive symptoms, rejection sensitivity, depressive symptoms, anxiety, and psychoticism (Markovitz et al., 1991). These improvements occurred regardless of whether subjects had a concurrent diagnosis of major depressive disorder. Such findings are limited by the fact that the study was open-label and by the heterogeneity of the subjects.

TABLE 28.3 Pharmacology of Impulsive Aggression and Borderline Personality Disorder: Antidepressants

Study	*Diagnosis*	*Study Design*	*Comment*
Soloff et al. (1986)	N = 52, BPD inpatients	Type 2 study: amitriptyline; placebo-controlled	AMI nonresponders showed significantly more impulsive/assaultive behavior than placebo nonresponders; AMI responders showed improvement in impulsive behavior and depression scores.
Parsons et al. (1989)	All patients had symptoms of atypical depression; Group 1: *n* = 40 patients with >5 *DSM-III* BPD criteria, *n* = 61 patients with >4 criteria; Group 2: *n* = 19 patients, BPD to a considerable extent, *n* = 29, patients BPD to only some extent as measured by the Personality Assessment Form	Type 1 study: double-blind, placebo-controlled; random assignment to phenelzine 60 mg or imipramine 200 mg for 3–6 weeks each medication	BPD patients with symptoms of atypical depression had significant improvement in CGI scores due to phenelzine vs. imipramine and placebo; imipramine was felt to be minimally effective.
Norden (1989)	N = 12 BPD patients, all except 1 with histories of suicidality	Type 3 study: fluoxetine; open-label	Very much or much improved; irritability and suicidality among the most responsive symptoms
Cornelius et al. (1991)	N = 5, BPD inpatients who had failed to respond to phenelzine and at least one neuroleptic	Type 3 study: fluoxetine; open-label	Decreases in impulsivity and suicidality
Markovitz et al. (1991)	N = 22 outpatients: 8 BPD, 10 SPD/BPD with mixed symptoms, 4 SPD; 13 patients also with MDD	Type 3 study: fluoxetine; open-label; 20–80 mg over 12 weeks sensitivity, psychoticism, anxiety, and obsessive-compulsive symptoms regardless of comorbid diagnosis of MDD	Decrease in 50% of patients' self-mutilatory behavior; significant decrease in depression, rejection
Soloff et al. (1993)	N = 92, BPD and mixed BPD/SPD features	Type 1 study: comparison between haloperidol and phenelzine; double-blind, placebo-controlled	Phenelzine was less effective than haloperidol in decreasing impulsivity/hostile-belligerence; phenelzine did not improve atypical depressive symptoms but did decrease scores on Buss-Durkee Hostility Inventory.
Coccaro & Kavoussi (1995)	N = 40 personality disorder patients with histories of impulsive aggression	Type 1 study: fluoxetine 20–60 mg; double-blind, placebo-controlled; 12 weeks	Overt aggression scores were reduced at weeks 4, 10, 12, and endpoint; irritability scores were reduced at weeks 6–12 and endpoint.
Salzman et al. (1995)	N = 22 patients recruited from the community (13 met BPD criteria and 9 had BPD traits); mild to moderate severity	Type 1 study: fluoxetine 20–60 mg; double-blind, placebo-controlled; 13 weeks including 1-week placebo lead-in	Anger and depression significantly declined more in the fluoxetine group than in the placebo group. Measures included PDRS anger and depression, POMS anger and depression, OAS anger against objects, and HAM-D scales.

TABLE 28.3 (continued)

Study	*Diagnosis*	*Study Design*	*Comment*
Rinne et al. (2002)	*N* = 38 BPD patients; moderate to severe pathology from outpatient clinic and newspaper referral	Type 1 study: fluvoxamine (150–200 mg/day); randomized placebo-controlled double-blind for 6 weeks; followed by single-blind half-crossover for 6 weeks and open- label for next 12 weeks	Significant improvement in rapid-mood shift subscale of BPD-SI (independent of comorbid affective disorders or posttraumatic stress disorder). No significant medication effect upon BPD-SI anger or impulsivity.
Simpson et al. (2004)	*N* = 25 female BPD patients in treatment in a 5-day DBT-based partial hospital program, dissociation or GAF	Type 1 study: fluoxetine (40 mg/day); randomized double-blind 12-week comparison of DBT + fluoxetine to DBT + placebo	No added benefit of fluoxetine over placebo in aggression, self-injury, suicidality, depression
New et al. (2004)	*N* = 20 BPD patients recruited from advertisements and clinic referral	Type 3 study: fluoxetine (20 mg/day); randomized double-blind placebo-controlled. Only 3 placebo subjects completed.	Significant improvement from baseline to completion in OAS-M aggression and irritability scores but not suicidality or depression
Taner et al. (2006)	*N* = 43 outpatients with atypical depression (54% with comorbid personality disorder, 8.21% with BPD)	8-week, single-blind randomized study of reboxetine (up to 10 mg/day) vs. fluoxetine (up to 40 mg/day)	Both reboxetine and fluoxetine were effective in reducing symptoms of depression, but more patients taking reboxetine dropped out due to side effects.
Bellino et al. (2010)	*N* = 18 patients with BPD	Open-label duloxetine (60 mg/day) for 12 weeks	Symptom improvement, decreased aggression and impulsivity
Dunlop et al. (2011)	*N* = 90 patients with MDD	Double-blind open-label sertraline (50–200 mg/day) combined with tri-iodothyronine (T3, double-blind) or matching placebo	Sertraline reduced maladaptive traits of impulsivity and externalization measured with the Psychopathic Personality Inventory.

AMI = amitriptyline; BPD = borderline personality disorder; BPD-SI = Borderline Personality Disorder Severity Scale; CGI = Clinical Global Impression; DBT = dialectical behavior therapy; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Rating Scale; MDD = major depressive disorder; OAS = McLean Hospital Overt Aggression Scale; PDRS = Personality Disorders Rating Scale; POMS = Profile of Mood States; SPD = schizotypal personality disorder.

There have been attempts to "pharmacologically distinguish" between affective and psychotic-like symptoms, primarily in BPD groups with some SPD patients included. In one large, mixed sample, amitriptyline led to a significant improvement in anxiety and hostility for the whole group, although less effectively than haloperidol (Soloff et al., 1989). Tranylcypromine was used in a primarily BPD group with a small subset of SPD patients and was found to decrease significantly a broad range of symptoms, including depressive scores, anxiety, rejection sensitivity, and impulsivity (Cowdry & Gardner, 1988). However, the generalized improvement failed to delineate a differential response of affective symptoms or psychotic-like symptoms to antidepressants in these patient populations. Thus, to determine the efficacy of antidepressants for SPD symptomatology, replication studies using double-blind, placebo-controlled methods in homogeneous groups of SPD patients are needed.

CLUSTER B DISORDERS ("DRAMATIC" CLUSTER)

The cluster B (dramatic) disorders are characterized by core dimensions of impulsivity/aggression and

affective lability. BPD and antisocial personality disorder are the prototype diagnoses involving these traits. Numerous studies have investigated the neurobiological substrates underlying each of these dimensions and the corresponding implications for pharmacological management of the disorders in this cluster.

Borderline Personality Disorder

The proposed traits that characterize BPD according to Section III of the *DSM-5* are based on the psychology literature and are derived from the Five Factor Model of personality (Costa & Widiger, 2002). The relation between Five Factor Model traits and *DSM-IV* personality disorders is supported by a growing body of data (Samuel & Widiger, 2008). The traits that characterize BPD according to *DSM-5* (negative affectivity, disinhibition, and antagonism) are closely linked to the core BPD traits of impulsive aggression and affective dysregulation, which have been consistently validated (Siever & Weinstein, 2009).

Affective Dysregulation and Impulsive Aggression Dimensions

Impulsive aggression and affective dysregulation have been associated with a number of determinants, including genetic factors, structural and functional brain abnormalities, and disturbances of neurotransmitter and neuropeptide systems.

Genetic Studies

Despite converging evidence from family, twin, and adoption studies supporting an underlying genetic vulnerability for BPD, the specific genetic underpinnings of BPD remain unexplored (Calati, Gressier, Balestri, & Serretti, 2013; Siever, Torgersen, Gunderson, Livesley, & Kendler, 2002b). There are only a few association studies, most of them in small samples, and their positive results remain largely unreplicated and have not been confirmed by meta-analyses (Calati et al., 2013).

BPD has heritability scores of 0.65 to 0.76 (Distel et al., 2008; New, Goodman, Triebwasser, & Siever, 2008; Torgersen et al., 2000) as estimated from twin studies. Moderate heritability has also been reported for dimensional BPD traits (Torgersen et al., 2008). Candidate genes for traits of impulsive aggression and emotional dysregulation include those that modulate the activity of neurotransmitters such as serotonin and catecholamines, as well as genes involved in neuropeptide systems (Siever, 2008; Siever & Weinstein, 2009).

Brain Abnormalities

Converging evidence supports a model of reduced prefrontal modulation of limbic structures (especially the amygdala and insula), which appear to be hyperreactive in patients with BPD, resulting in affective dysregulation and aggression (Bohus, Schmahl, & Lieb, 2004; Mauchnik & Schmahl, 2010).

Consistent with this model, structural brain imaging studies have reported abnormalities in the volumes and white matter integrity/connectivity of frontal and limbic regions. One of the most consistent structural findings in patients with BPD compared to healthy controls is a decrease in volume in the anterior cingulate gyrus (Hazlett et al., 2005; Minzenberg, Fan, New, Tang, & Siever, 2008; Soloff, Nutche, Goradia, & Diwadkar, 2008; Tebartz van Elst et al., 2003), especially in men (Soloff et al., 2008; Vollm et al., 2009). Other structural abnormalities in BPD include lower volumes in hippocampus (Brambilla et al., 2004; Irle, Lange, & Sachsse, 2005; Nunes et al., 2009; Ruocco, Amirthavasagam, & Zakzanis, 2012; Zetzsche et al., 2007), orbital frontal cortex (Tebartz van Elst et al., 2003), amygdala (Nunes et al., 2009; Ruocco et al., 2012; Tebartz van Elst et al., 2007), and surrounding areas of the temporal lobe (Goethals et al., 2005). Some but not all studies (de-Almeida et al., 2012; Ruocco et al., 2012) have raised the possibility that the smaller volumes in BPD may relate to comorbidity with posttraumatic stress disorder (PTSD) or a history of trauma for hippocampal volume (Nunes et al., 2009; Schmahl et al., 2009; Weniger, Lange, Sachsse, & Irle, 2009) and with major depressive disorder for amygdala volume (Zetzsche et al., 2006). Diffusion tensor imaging (DTI) studies also have found altered white matter tract integrity in the orbital frontal cortex (Grant et al., 2007) and diminished interhemispheric structural connectivity between both the left and right anterior cingulate gyrus in BPD (Rusch et al., 2010). This is consistent with the above model

of altered fronto-limbic circuitry in BPD, which has also been studied with functional neuroimaging methods as described below.

Many studies have consistently found decreased activation of prefrontal areas involved in emotion control in BPD. For example, early positron emission tomography (PET) imaging studies found lower activity of orbital frontal cortex and anterior cingulate gyrus in BPD compared to controls (Goyer et al., 1994; Leyton et al., 2001; New et al., 2002; Siever et al., 1999; Soloff, Meltzer, Greer, Constantine, & Kelly, 2000). More recently, a PET study of laboratory-induced aggression using the Point Subtraction Aggression Paradigm reported that BPD patients with high levels of impulsive aggression showed increased relative glucose metabolic rate in orbital frontal cortex and amygdala in response to provocation, but not in more dorsal brain regions involved in top-down control of aggression and of emotion (New et al., 2009). In contrast, healthy individuals did activate dorsal, cognitive control regions of prefrontal cortex during aggression provocation (New et al., 2009). Poor coupling between orbital frontal cortex and amygdala has also been reported in association with aggression (New et al., 2007).

Decreased prefrontal activation in BPD has also been shown by most functional magnetic resonance imaging (fMRI) studies using emotional stimuli, with some exceptions (Minzenberg, Fan, New, Tang, & Siever, 2007; Schmahl et al., 2006; Schnell, Dietrich, Schnitker, Daumann, & Herpertz, 2007). The majority of studies have shown less activation (or more deactivation) of orbital frontal cortex or anterior cingulate gyrus in BPD compared to healthy controls in response to emotional stimuli (Koenigsberg et al., 2009; Kraus et al., 2009; Schmahl et al., 2003; Schnell et al., 2007; Silbersweig et al., 2007; Wingenfeld et al., 2009) and to physical pain (Minzenberg et al., 2007; Schmahl et al., 2006; Schnell et al., 2007), although one study showed increased anterior cingulate gyrus activation to negative pictures in BPD (Minzenberg et al., 2007) and one to unresolved conflicts (Beblo et al., 2006).

Functional neuroimaging studies also suggest that amygdala and insula have abnormal activity (Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013) in BPD. Several studies, but not a recent meta-analysis (Ruocco et al., 2013), have shown increased amygdala activation to emotional stimuli (e.g., emotional pictures and faces) in BPD (Beblo et al., 2006; Donegan et al., 2003; Koenigsberg et al., 2009; Schulze et al., 2011). However, amygdala activity decreases in response to pain in BPD (Kraus et al., 2009; Niedtfeld et al., 2010; Schmahl et al., 2006).

In summary, in BPD patients, prefrontal brain regions that normally control emotional expression and aggression (e.g., orbital frontal cortex and anterior cingulate gyrus) may fail to activate during emotional provocation, while limbic regions (e.g., amygdala and insula) hyperreact to emotional probes. However, these findings potentially lack specificity, since many of the circuits implicated in BPD appear to be involved in other psychiatric disorders, including major depressive disorder (Davidson, Irwin, Anderle, & Kalin, 2003), bipolar disorder (Blumberg et al., 2003) and PTSD (Shin et al., 1999).

Neurotransmitter and Neuropeptide Systems

Studies probing the serotonergic system suggest that the model of decreased prefrontal regulatory control and increased limbic reactivity described above may relate to altered serotonergic facilitation of "top-down" control. Decreased serotonergic indices have been implicated in impulsive/aggressive behavior toward the self (i.e., suicide attempts) or others across diagnostic categories, supporting the conceptualization of impulsivity/aggression as a dimensional trait. For example, early cerebrospinal fluid studies found decreased levels of 5-hydroxyindolacetic acid—a serotonin metabolite—in subjects with a history of suicide attempts (Asberg & Traskman, 1981; Asberg, Traskman-Benz, & Thoren, 1976) or impulsive aggressive behavior (Coccaro, 1989). Since then, numerous studies employing a wide variety of methods have replicated the finding of decreased serotonergic function in BPD (Coccaro et al., 1989; Dougherty, Bjork, Huckabee, Moeller, & Swann, 1999; O'Keane et al., 1992), including neuroimaging studies using pharmacological probes of serotonin (Leyton et al., 2001; New et al., 2002, 2004; Siever et al., 1999; Soloff et al., 2000). Patients with personality disorders and impulsive aggression showed lower serotonin transporter availability compared with healthy controls, as measured by the PET ligand, [11C]McN 5652, in anterior cingulate gyrus (Frankle et al., 2005). Moreover, fluoxetine treatment enhances metabolic activity in orbital frontal cortex and anterior cingulate gyrus in impulsive aggressive individuals, which is associated

with symptomatic improvement (New et al., 2004). These studies provide strong neurobiological support for the use of selective serotonin reuptake inhibitors (SSRIs) to treat impulsivity/aggression in BPD.

Noradrenergic and cholinergic systems, which appear to play key roles in the genesis of mood disorders, have also been a logical area of study in the personality disorders. Initial investigations suggested that the transient dysphoria seen in BPD patients could be related to excessive cholinergic availability (Steinberg et al., 1997) and that hyperreactivity of the central adrenergic system may be involved in affective instability in BPD and other personality disorders (Southwick, Yehuda, Giller, & Perry, 1990).

Neuropeptides such as oxytocin are an area of growing interest in BPD. It has been suggested that deficits in the attachment and affiliative systems modulated by oxytocin may underlie the impulsive aggressive reactions to perceived rejection and loss that are common in BPD (Stanley & Siever, 2010). Because of its anxiolytic and prosocial effects (Macdonald & Macdonald, 2010; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011; Zink & Meyer-Lindenberg, 2012), oxytocin has been suggested as a promising treatment for patients with disorders associated with severe deficits in social interactions, such as BPD (Meyer-Lindenberg et al., 2011). In BPD, preliminary data indicate similar stress-reducing effects of oxytocin (Simeon et al., 2011) and suggest that it modulates amygdala activity for optimal social cognitive functioning (Herpertz, Lischke, Berger, & Gamer, 2012)—that is, compensating for the hypersensitivity to social threat and amygdala hyperreactivity seen in BPD.

Given the high theoretical interest in the oxytocinergic system in BPD (Stanley & Siever, 2010), it is surprising that research examining the genetics of the oxytocinergic system in BPD populations is lacking. However, there is some evidence from genetic studies suggesting that the oxytocinergic system is involved in some of the core dimensions of BPD, such as interpersonal dysfunction and impulsive aggression. For example, oxytocin receptor gene (OXTR) polymorphisms have been linked to trait empathy (Wu, Li, & Su, 2012), aggressive behavior, the propensity to react to situations with elevated levels of anger (Johansson et al., 2012), and prosocial temperament (Tost et al., 2010). Oxytocin gene polymorphisms have been associated with aggressive-antisocial behaviors in children (Malik, Zai, Abu, Nowrouzi, & Beitchman, 2012) and with interindividual differences in dopaminergic responses to stress (Love et al., 2012). Moreover, OXT gene-knockout mice display exaggerated aggressive behavior (Ragnauth et al., 2005). However, there are no published genetic studies of oxytocinergic system genes in BPD. We have found a novel oxytocin haplotype, which is associated with aggression, attachment, and impulsivity, in a sample enriched for patients with personality disorders (Perez-Rodriguez et al., 2013).

Since opioids are also involved in social attachment, a deficit in endogenous opiates may underlie the interpersonal difficulties characteristic of BPD. One recent PET study (Prossin, Love, Koeppe, Zubieta, & Silk, 2010) measured mu-opioid receptor binding by using the mu-opiate ligand [^{11}C] carfentanil in patients with BPD during induction of neutral and sad sustained emotional states (Prossin et al., 2010). The study found greater baseline mu-opioid receptor availability in BPD, which may suggest a deficit in endogenous opioids. These results also suggest that BPD patients increase endogenous opiate availability more than controls during sad mood induction, which might reflect a compensatory response (Stanley et al., 2010; Stanley & Siever, 2010). In fact, one theory about self-cutting, a behavior common in BPD, is that it represents a method of releasing endogenous opioids to compensate for an intrinsic opioid deficit (New & Stanley, 2010; Stanley & Siever, 2010). We have found that polymorphisms of the mu-opioid receptor may be associated with affective instability and BPD (Siever et al., unpublished data). These associations seem to be potentiated by trauma, underscoring the interactive effects of genetics and environment.

Pharmacology of Borderline Personality Disorder

Antidepressants

Neurobiological evidence of blunted serotonergic systems in impulsivity/aggression and BPD would suggest that antidepressant medications enhancing serotonergic function may play an important role in the treatment of BPD. However, in the past decade of psychopharmacological research in BPD patients, there has been a shift from antidepressants to mood stabilizers and antipsychotics.

In fact, although SSRIs were traditionally considered the first-line treatment for BPD, several recent meta-analyses and reviews have concluded that antidepressants, including SSRIs and tricyclics, have the least effect on BPD symptoms, compared to mood stabilizers and antipsychotics (Abraham & Calabrese, 2008; Feurino & Silk, 2011; Ingenhoven, Lafay, Rinne, Passchier, & Duivenvoorden, 2010; Lieb, Vollm, Rucker, Timmer, & Stoffers, 2010; Mercer, Douglass, & Links, 2009; Stoffers et al., 2010). Antidepressants may have a role in reducing anxiety and impulsivity/aggression (Ingenhoven et al., 2010; Mercer et al., 2009) and in the presence of comorbid conditions such as major depression (Stoffers et al., 2010).

Studies of antidepressant agents in BPD are hampered by specific methodological challenges. First, there are very high rates of comorbidity between BPD and depressive disorders (Grant et al., 2008; Lenzenweger et al., 2007; Skodol et al., 2002, 2005). Moreover, the affective symptoms in BPD are closely related to those found in depressive disorders. A summary of antidepressant trials in the treatment of BPD can be found in Table 28.3.

Antipsychotics

Early studies of typical antipsychotic medication use for BPD (see Table 28.1) showed global but modest improvement in symptoms, including impulsivity, depression, suicidal ideation, rejection sensitivity, and psychotic-like symptoms, such as paranoid ideation, ideas of reference, and derealization (Soloff et al., 1989).

More recently, several studies have examined the effectiveness of SGAs. Olanzapine has now been studied in several open-label studies (Damsa et al., 2007; Shoja-Shafti, 2006; Zanarini et al., 2012) and randomized, double-blind trials (Schulz et al., 2008; Shafti & Shahveisi, 2010; Soler et al., 2005; Zanarini & Frankenburg, 2001; Zanarini et al., 2004, 2011). Most but not all (Schulz et al., 2008) of these studies find that olanzapine is effective in treating anger/aggression in BPD, and several studies report that olanzapine treats depression and anxiety as well. Olanzapine also appears to reduce interpersonal sensitivity and paranoia (Zanarini & Frankenburg, 2001). One study found that the combination of olanzapine and fluoxetine was less effective than olanzapine alone in treating the dysthymia characteristic of BPD (Zanarini et al., 2004). Injectable olanzapine has been used to reduce agitation in several open-label studies and case series in emergency room settings (Damsa et al., 2007; Pascual et al., 2006). All studies reported weight gain with olanzapine, and two recorded mean gains of greater than 6 lbs over a period of 12 weeks. These weight gains are likely to be troublesome to many borderline patients and may reduce their acceptance of the drug. Zanarini and colleagues (2004) reported less weight gain from combined treatment with olanzapine and fluoxetine than from olanzapine alone.

An open-label, uncontrolled trial of risperidone found it to be effective in reducing hostility, suspicion, and depression in BPD patients and did not report weight gain as a side effect (Rocca, Marchiaro, Cocuzza, & Bogetto, 2002). A more recent open-label study of 8 weeks of risperidone (up to 2 mg/day) found global symptom improvement across BPD-relevant domains, including affective dysregulation, cognitive impairment, impulsivity, and disturbed relationships, but a mean weight gain of 3.7 lbs was observed (Friedel et al., 2008). Depot formulations of risperidone have shown improvement in long-term symptom severity and functioning in an open-label study (Carrasco, Palomares, & Marsa, 2012).

A first open-label trial of quetiapine (with a high dropout rate of 33%) reported significant improvement from baseline levels in impulsivity, hostility, anxiety, depression, and social and global functioning, but not hopelessness, in a group of markedly to severely symptomatic BPD clinic outpatients (Villeneuve & Lemelin, 2005). More recent open-label trials of quetiapine observed symptom improvement across several domains, including global functioning, depressive symptoms, affect lability, global severity, impulsivity and anger/hostility, and anxiety (Adityanjee et al., 2008; Bellino, Paradiso, & Bogetto, 2006; Perrella, Carrus, Costa, & Schifano, 2007; Roepke et al., 2008; Van den Eynde et al., 2008).

A randomized, double-blind, placebo-controlled study reported an effect of aripiprazole in decreasing BPD symptoms, including depressive and anxiety symptoms, and anger. This improvement was sustained at an 18-month follow-up (Nickel, Loew, & Pedrosa Gil, 2007; Nickel et al., 2006).

Two open-label studies have examined the effect of the atypical antipsychotic medication clozapine. In a study of 12 BPD inpatients with severe psychotic-like

symptoms (Benedetti et al., 1990), low-dose clozapine treatment was associated with a decrease in psychotic-like symptoms, suicide attempts, physical fights, and depression. A retrospective mirror-image open-label chart review study (Chengappa, Ebeling, Kang, Levine, & Parepally, 1999) of the treatment of seven inpatients meeting criteria for BPD, six of whom also had psychotic disorder diagnoses, found a decrease in self-mutilation, seclusion, and use of antianxiety medications and an increase in Global Assessment of Functioning (GAF) score. It is not possible to determine whether the improvements were due to the effect of clozapine on BPD or on the comorbid disorder. Because of the risk of agranulocytosis, it is prudent to reserve trials of clozapine at present for the most severely symptomatic BPD patients who have psychotic symptoms and have not responded to other SGAs.

In summary, evidence from meta-analyses, double-blind, randomized clinical trials and open-label studies suggests that treatment with antipsychotics may be effective for treating core symptoms of BPD, including mood lability/affective dysregulation, anger and impulsive-behavioral dyscontrol, and cognitive-perceptual symptoms (Feurino & Silk, 2011; Ingenhoven & Duivenvoorden, 2011; Lieb et al., 2010; Mercer et al., 2009; Stoffers et al., 2010; Vita, De Peri, & Sacchetti, 2011).

Mood Stabilizers

The prominence of impulsive aggression and mood instability in BPD suggests that mood stabilizers may be valuable treatment options.

Lithium has been shown to decrease irritability, suicidality, and angry behavior, as rated by the treating therapist, in a cohort of borderline subjects (Links et al., 1990). Interestingly, there was a clear trend in this study for lithium to be more effective than desipramine (a noradrenergic agent) in decreasing anger and suicidality, as well as depression.

The use of carbamazepine for patients with behavioral dyscontrol/impulsivity or borderline patients has yielded mixed results in placebo-controlled trials. Carbamazepine has been found to decrease assaultiveness and depression significantly in patients with frontal lobe dysfunction (Foster, Hillbrand, & Chi, 1989) and was initially found to improve impulsivity and behavioral dyscontrol among BPD patients (Cowdry & Gardner, 1988). However, this finding was not replicated in a later study, which suggested that carbamazepine may have no effect on dyscontrol and may in fact be associated with an increase in impulsive, violent behavior in some BPD subjects (de la Fuente & Lotstra, 1994). In comparison to propranolol, use of carbamazepine may be associated with a decrease in aggression in patients with intermittent explosive disorder (Mattes, 1990), although both medications tend to lead to fewer aggressive outbursts. In this study, however, subjects also received antipsychotic agents, other anticonvulsants, and antidepressants, limiting the applicability of the findings. A 12-week open-label trial of oxcarbamazepine, a chemical analogue of carbamazepine that is less likely to cause blood dyscrasias, autoinduce its own metabolism, or interact with other drugs, found a statistically significant improvement in ratings of impulsivity, anger outbursts, affective instability, interpersonal sensitivity, anxiety, Brief Psychotic Rating Scale (BPRS) score, and Clinical Global Impression-Severity score (Bellino, Paradiso, & Bogetto, 2005; Table 28.4). However, 25% of patients dropped out by the fourth week for nonadherence.

The mood stabilizer most extensively studied in the BPD population is divalproex sodium. An early open-label 8-week trial (Stein, Simeon, Frenkel, Islam, & Hollander, 1995) of divalproex in 11 patients meeting *DSM-III-R* criteria for BPD showed an overall improvement in half of the sample, with modest beneficial effects on anger, impulsivity, irritability, and rejection sensitivity. A subsequent small, 10-week, double-blind, placebo-controlled study of divalproex sodium (Hollander et al., 2001) found a significant improvement in Clinical Global Impression (CGI) score and Global Assessment Scale (GAS) scores among the six patients who completed treatment. The study was limited by the premature dropout of all four placebo-treated patients and 50% of the divalproex-treated patients. Impulsiveness in this patient population contributed to the high dropout rate, rather than medication side effects, highlighting the challenge in conducting treatment studies of impulsive patients. A somewhat larger placebo-controlled, double-blind study of female BPD patients with comorbid bipolar disorder (Frankenburg & Zanarini, 2002) found divalproex sodium to be superior to placebo in reducing anger, hostility, aggression, and interpersonal sensitivity. Because these patients all met criteria for bipolar disorder, it remains unclear

TABLE 28.4 Pharmacology of Impulsive Aggression and Borderline Personality Disorder: Mood Stabilizers/Anticonvulsants

Study	*Diagnosis*	*Study Design*	*Comment*
Sheard et al. (1976)	N = 66, inmates characterized by extreme impulsivity, aggression, and hostility	Type 2 study: lithium vs. placebo	Decrease in number of major prison infractions
Links et al. (1990)	N = 15 BPD	Type 1 study: lithium vs. desipramine; double-blind, placebo-controlled	Lithium led to decrease in therapist's perception of patient irritability, anger, and suicidal symptoms; trend for desipramine to have no effect or to worsen symptoms of anger/suicide and to be less effective than lithium in decreasing depression scores.
Hollander et al. (2001)	N = 16 BPD patients referred clinically and from advertisements	Type 2 study: divalproex (mean blood level 64.6 micrograms/mL); 10-week randomized double-blind placebo-controlled trial	50% dropout rate in divalproex group, 100% in placebo group; among completers 5/6 were responders based on CGI.
Frankenburg & Zanarini (2002)	N = 20 female BPD patients who also met *DSM-IV* criteria for bipolar II disorder	Type 2 study: divalproex (mean dose 850 mg/day); 6-month randomized double-blind placebo-controlled trial	Divalproex superior to placebo for SCL-90 anger/hostility and interpersonal sensitivity and OAS-M aggression; 50% dropout in divalproex group by week 12
Hollander et al. (2003, 2005)	N = 96 cluster B personality disorder patients (including 52 with BPD); *n* = 34 PTSD and *n* = 116 IED patients	Type 1: divalproex (mean dose 1,404 mg, blood level 65.5 micrograms/mL); randomized multicenter 12-week double-blind placebo-controlled trial	For cluster B, divalproex superior to placebo in OAS-M aggression, verbal assault, assault against objects, assault against others, irritability scales, and CGI-S; no significant effect of diavalproex on aggression for the IED or PTSD patients
Nickel et al. (2004)	N = 29 female BPD patients recruited by advertisement who had subjective feelings of "constantly increasing anger"	Type 1: topiramate (dose titrated to 250 mg/day by week 6); 8-week randomized double-blind placebo-controlled trial	Topiramate superior to placebo on STAXI anger-out, anger-control, state anger, and trait anger, but not anger-in scales
Nickel et al. (2005)	N = 42 male BPD patients meeting criteria of Nickel et al. (2004), above	Type 1: topiramate same as Nickel et al. (2004), above	Topiramate superior to placebo on STAXI anger-out, anger-control, state anger, and trait anger, but not anger-in scales. Improvement was sustained after 18-month follow-up (Nickel & Loew, 2008).

(*continued*)

TABLE 28.4 (continued)

Study	*Diagnosis*	*Study Design*	*Comment*
Tritt et al. (2005)	N = 24 female BPD patients	Type 2: lamotrigine; 8-week double-blind placebo-controlled trial	Lamotrigine superior to placebo on STAXI anger-out, anger-control, state anger, and trait anger, but not anger-in scales. Improvement on aggression measures remained significant at an 18-month follow-up after study completion (Leiberich et al.. 2008).
Bellino et al. (2005)	N = 17 clinic outpatients meeting criteria for BPD	Type 3: oxcarbamazepine (mean dose 1,315 mg); 12-week open-label design	Significant improvement in impulsivity, affective instability, anger outbursts, interpersonal sensitivity, anxiety, CGI-S, but not depression or social-occupational functioning
Simeon et al. (2007)	N = 20 BPD outpatients	Open-label 12 weeks of divalproex extended-release	Significant improvement on the CGI-I, the Global Assessment Scale, the OAS-M irritability subscale, and the Aggression Questionnaire
Loew et al. (2006)	N = 56 females with BPD	Randomized, double-blind trial; 10 weeks of topiramate (up to 200 mg/day) vs. placebo	Improvement across symptom domains (Symptom-Checklist), health-related quality of life (SF-36 Health Survey), and interpersonal functioning (Inventory of Interpersonal Problems)
Reich et al. (2009)	N = 28 subjects with BPD	Randomized, double-blind trial; 12 weeks of lamotrigine (flexible dose; mean final dose = 106.7 mg/day) vs. placebo	Significantly greater symptom improvement (ALS affective lability scores and ZAN-BPD affective lability and impulsivity scores).
Moen et al. (2012)	N = 15 patients with BPD who had SCL-90 scores >150 after 4 weeks of "condensed DBT"	Randomized to 12 weeks of double-blind divalproex extended-release vs. placebo	No significant differences between the participants assigned to divalproex extended-release vs. placebo

ALS = Affect Lability Scale; BPD = borderline personality disorder; CGI-S = Clinical Global Impression-Severity; DBT = dialectical behavior therapy; IED = intermittent explosive disorder; OAS-M = Overt Aggression Scale Modified; PTSD = posttraumatic stress disorder; SCL-90 = Hopkins Symptom Check List 90; STAXI = State-Trait Anger Expression Inventory; ZAN-PBD = Zanarini Rating Scale for Borderline Personality Disorder.

whether the divalproex was treating the BPD or the bipolar disorder. A type 1 multisite, randomized, double-blind, placebo-controlled study of the efficacy of divalproex sodium in treating aggression in cluster B personality disorders (including BPD), intermittent explosive disorder, and PTSD represents the largest study of this medication in the treatment of BPD (Hollander et al., 2003). Although no effect of divalproex sodium in reducing aggression was reported for the sample taken as a whole, a post hoc analysis of the 96 cluster B personality disorder patients (52 of whom met criteria for BPD) showed that divalproex

sodium was superior to placebo in reducing aggression, verbal assault, assault against objects, and irritability and in improvement on the CGI severity scale. In this study, too, the dropout rate among the patients with cluster B personality disorders was close to 50% for both the placebo and divalproex groups. In a post hoc follow-on report, Hollander, Swann, Coccaro, Jiang, and Smith (2005) examined the response of the 52 individuals with BPD in more detail. They found that divalproex sodium was superior to placebo in reducing the Overt Aggression Scale aggression score when baseline aggression, impulsiveness, hypomania, and depression were entered as covariates. Moreover, baseline trait impulsivity and state aggression, but not trait aggression or hypomania, predicted treatment response to divalproex sodium. A recent double-blind, randomized, placebo-controlled trial in a small sample of patients who did not respond to dialectical behavioral therapy found no differences in the effects of divalproex extended-release compared to placebo (Moen et al., 2012), and another small open-label study found improvements in global severity and aggression (Simeon, Baker, Chaplin, Braun, & Hollander, 2007).

Three studies of the efficacy of topiramate in female and male BPD patients have been reported (Loew et al., 2006; Nickel et al., 2004, 2005). For both female and male patients, topiramate was associated with greater improvement across multiple symptom domains of the Symptom Checklist (SCL-90-R scale), including somatization, interpersonal sensitivity, anxiety, anger/hostility, phobic anxiety, and Global Severity Index. Patients also experienced significant improvements on all eight scales of health-related quality of life (measured with the SF-36 Health Survey) and in interpersonal functioning (Inventory of Interpersonal Problems). Topiramate is an attractive candidate for treating BPD because, unlike many of the other promising medications for BPD, which are associated with weight gain, topiramate was associated with modest weight loss (Loew et al., 2006). This should increase its acceptability in this population.

A case report series (Pinto & Akiskal, 1998) first described the open-label use of lamotrigine, the anticonvulsant and mood stabilizer, in eight severely disabled BPD patients who did not meet criteria for any concurrent major mood disorder. Three of the eight patients showed a dramatic improvement, with disappearance of suicidal, impulsive, sexual, and drug-taking behaviors, and no longer met BPD criteria at an average follow-up of 1 year. Two randomized, double-blind, placebo-controlled studies of lamotrigine in male and female BPD patients have been reported (Reich, Zanarini, & Bieri, 2009; Tritt et al., 2005). Lamotrigine was superior to placebo in reducing anger, affective lability, and impulsivity and did not cause clinically significant weight gain.

In a recent meta-analysis, mood stabilizers, with the exception of valproic acid, were found to have a large pooled effect size for treatment of anger symptoms. Valproic acid and carbamazepine also had a moderate effect on depression (Mercer et al., 2009). However, a more recent Cochrane systematic review on the use of antiepileptics for aggression and impulsivity concluded that there is not sufficient evidence to allow any firm conclusion to be drawn (Huband, Ferriter, Nathan, & Jones, 2010). Based on the results of individual studies, the authors found some evidence that valproic acid was superior to placebo for outpatient men with recurrent impulsive aggression and for impulsively aggressive adults with cluster B personality disorders; carbamazepine was superior to placebo in reducing acts of self-directed aggression in women with BPD; oxcarbazepine was superior to placebo for verbal aggression and aggression against objects in adult outpatients; and phenytoin was superior to placebo on the frequency of aggressive acts in male prisoners and in outpatient men with personality disorder (Huband et al., 2010).

Novel Agents

Despite evidence of increased noradrenergic activity in irritable or emotionally unstable patients with BPD, there are few BPD treatment studies of medications that directly target this system. Philipsen and colleagues (2004) examined for the first time the acute effect of clonidine, an alpha-2 agonist with peripheral and central activity that reduces norepinephrine release, in 14 female symptomatic BPD inpatients (Philipsen et al., 2004). Patients were instructed to notify staff at times of "strong aversive inner tension," at which point they would be administered clonidine 75 mcg or 150 mcg in a single-blind, randomized design. On the next occasion that they notified staff of high tension, they received whichever dose they had not received on the first occasion.

Self-report ratings of aversive inner tension, the urge to commit self-injurious behavior, dissociative symptoms, and suicidal ideation were obtained prior to drug administration and at 30-minute intervals for the next 2 hours. Repeated-measures ANOVAs showed a significant effect for time in all four measures. There was no main effect for dose (75 mcg vs. 150 mcg). Although this study is strongly limited by the lack of a placebo control or a blind to active treatment, it provided support for further investigation of alpha-2 agonists in the treatment of BPD. A more recent double-blind, randomized crossover study of clonidine versus placebo in patients with BPD and a hyperarousal syndrome, with or without comorbid PTSD, found that hyperarousal improved regardless of PTSD comorbidity (Ziegenhorn et al., 2009) (Table 28.2).

Following reports that omega-3 fatty acids may be effective adjunctive treatments for bipolar disorder or depression, Zanarini and Frankenburg (2003) administered 1 g of the omega-3 fatty acid ethyl-eicosapentaenoic acid (E-EPA) or placebo in an 8-week randomized, double-blind design to 30 female BPD subjects. E-EPA was superior to placebo at the 8-week point in improvement in scores on the Modified Overt Aggression Sale and the Montgomery-Asberg Depression Rating Scale. There were no clinically significant side effects, and 90% of the subjects in both groups completed the study. More recently, a randomized double-blind, placebo-controlled 12-week trial reported that a dosage of 1.2 g/day long-chain omega-3 polyunsaturated fatty acids (PUFAs) was superior to placebo in improving global functioning (GAF), symptoms of depression (Montgomery-Asberg Depression Rating Scale), and PANSS negative symptoms, suspiciousness, tension, and poor impulse control on the PANSS (Amminger et al., 2013).

Other drug classes that have been investigated in clinical trials and single-dose studies in BPD patients, but for which evidence is still very limited, include corticosteroids (Wingenfeld et al., 2013), intranasal oxytocin (Bartz et al., 2011; Bertsch et al., 2013; Brune et al., 2013; Ebert et al., 2013; Simeon et al., 2011), opioid modulators such as naltrexone (an opioid-receptor antagonist) (Bohus et al., 1999; Schmahl et al., 2012), the stimulant methylphenidate (Golubchik, Sever, Zalsman, & Weizman, 2008), and the traditional Chinese herbal medicine *yi-gan san* (Miyaoka et al., 2008).

Overview of the Pharmacotherapy of Borderline Personality Disorder

In the past decade there has been an advance in the number and quality of studies of the pharmacotherapy of BPD, with the publication of a growing number of type 1 randomized, placebo-controlled, double-blind studies of reliably defined and well-characterized patient populations, and several reviews and meta-analyses (Bellino, Rinaldi, Bozzatello, & Bogetto, 2011; Binks et al., 2006; Feurino & Silk, 2011; Grootens & Verkes, 2005; Herpertz et al., 2007; Ingenhoven & Duivenvoorden, 2011; Kapoor, 2009; Lieb et al., 2010; Mercer et al., 2009; Paris, 2009, 2011; Ripoll, 2012; Ripoll, Triebwasser, & Siever, 2011; Saunders & Silk, 2009; Stoffers et al., 2010; Vita et al., 2011). Placebo-controlled trials are particularly important in this area because of the high placebo response rate of BPD patients.

However, the latest Cochrane review and meta-analysis reported that pharmacotherapy in BPD is not yet based on robust evidence from trials, with "very sparse" RCT evidence and "only a few study results per comparison, with small numbers of included participants." They concluded that there is support for the use of SGAs, mood stabilizers, and omega-3 fatty acids, but these require replication since most effect estimates were based on single-study effects. They also pointed out that there is no evidence from RCTs that any drug decreases overall BPD severity, rather than specific symptom dimensions.

Specifically, evidence is emerging that supports the efficacy of the SGA aripiprazole in reducing interpersonal problems, impulsivity, anger, psychotic paranoid symptoms, depression, anxiety, and general psychiatric pathology (Stoffers et al., 2010). For olanzapine, while no significant effects were detected for any primary outcomes, secondary analyses showed significant decreases in affective instability, anger, psychotic paranoid symptoms, and anxiety. Unfortunately, weight gain with this medication may be problematic for some patients and may affect patient acceptability. Interestingly, tolerability (rate of noncompleters) did not differ between the drug and placebo arms for any of the drugs studied (Stoffers et al., 2010).

Anticonvulsant mood stabilizers also appear to be quite promising. Valproate had significant effects in improvement of interpersonal problems, depression, and anger. Lamotrigine was significantly superior to placebo in reducing impulsivity and anger.

Topiramate had significant effects on interpersonal problems, impulsivity, anger, anxiety, and general psychiatric pathology. Topiramate may have particularly high patient acceptability because it is not associated with weight gain, but rather with modest weight loss. Regarding antidepressants, there was only a significant effect for the tricyclic amitriptyline on depressive symptoms, but there were no significant effects for mianserin, the SSRIs fluoxetine and fluvoxamine, or the MAOI phenelzine sulfate. Omega-3 fatty acids were found to have a significant effect on suicidality and depressive symptoms (Stoffers et al., 2010).

Based on their Cochrane review findings, Stoffers and colleagues (2010) make the following recommendations:

1. Pharmacological treatment of BPD should be targeted at defined symptoms.
2. Treatment with a given drug should last a sufficient period of time (according to the pharmacokinetic and dynamic properties of the drug) to judge if there are any benefits, but should be stopped or changed if there are none.
3. Polypharmacy is not supported by the RCT evidence and should be avoided whenever possible.
4. Special attention should be paid to toxic effects in case of overdosing (e.g., tricyclic antidepressants) and the potential for misuse or substance dependence (e.g., hypnotics and sedatives).
5. In the presence of a comorbid eating disorder, weight-related side effects (especially weight gain with olanzapine treatment and weight loss with topiramate treatment) should be taken into account (Stoffers et al., 2010).

CLUSTER C ("ANXIOUS" CLUSTER)

The psychobiology of anxiety (cluster C) has been investigated in greater depth. The guiding principle for much of the research is the assumption that the biological factors regulating anxiety provide a common basis for the anxiety spectrum disorders, superseding Axis I and Axis II distinctions.

There have been no pharmacotherapy trials involving the anxious cluster disorders. A limited number of controlled studies have looked at avoidant personality traits in patients with social phobia (see Herpertz et al., 2007, and Ripoll et al., 2011, for a review), whereas the use of medications for avoidant personality disorder alone has been documented only in case reports. Several medications have been tested and shown to be effective for social phobia, including MAOIs, the benzodiazepine clonazepam, and antidepressants. Among the latter, paroxetine, sertraline, and extended-release venlafaxine are approved by the FDA for the treatment of social phobia.

Case reports have described the usefulness of the MAOIs phenelzine and tranylcypromine for subjects with avoidant personality disorder: After 4 to 6 weeks of treatment, patients experienced marked improvements in their abilities to socialize. These gains were maintained at a 1-year follow-up when the patients continued to take the medications (Deltito & Stamm, 1989). Two case reports document the efficacy of fluoxetine for avoidant personality disorder (Deltito & Stamm, 1989; Goldman & Grinspoon, 1990). Within several weeks of initiating treatment, subjects reported decreases in social sensitivity and improvements in socialization, self-confidence, and assertiveness. Further controlled studies with well-defined groups of avoidant personality disorder and other anxious-cluster subjects are needed to establish the clinical indications for pharmacotherapy in this group of patients.

CONCLUSION

Despite significant advances over the past decade, research into the psychopharmacology and neurobiology of personality disorders is still in its infancy compared to other psychiatric disorders. The number of clinical trials is limited, and many have small sample sizes. Taken together, the evidence for symptom improvement is modest across personality disorders. However, despite the lack of FDA approval, drugs are used widely to treat personality disorders, particularly BPD. Therefore, it is critical to develop novel, more effective treatments grounded in better understanding of the neurobiology of the personality disorders.

Future research should be aimed toward fractionating the personality disorders into objectively measurable dimensions of psychopathology, such as affective lability or impulsive aggression, and examining their underlying neurobiology through the integration of multimodal levels of analysis, such as structural and functional neuroimaging, psychophysiology, and genetics, to name a few. These integrated multimodal measures should serve as outcome

measures for further controlled clinical trials to test the efficacy of new medications.

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